Implementation Guide

**Warfarin - Antidepressants**

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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# Introduction

## Background

Ensuring that drug-drug interaction (DDIs) alerts are effective and meaningful is a longstanding clinical informatics issue, with alert fatigue serving as an issue that can negatively impact clinician response and patient safety. Existing alerting systems for DDIs are often simplistic in nature or do not take the specific patient and pharmacological contexts into consideration, leading to false or overly sensitive alerts.

## Audience, Purpose, and Scope of this Implementation Guide

This document is designed to assist developers, clinicians, and pharmacists in applying this artifact toward enhancing clinical decision support (CDS) for potential drug-drug interactions between warfarin and antidepressants.

# Implementing and Using This Artifact

## Description and Purpose of the artifact

This artifact aims to address risks of bleeding that arise with concurrent use of the drugs warfarin and antidepressants. Depression, anxiety, atrial fibrillation (AF), cardiovascular disease, and thromboembolic disorders often coexist in patients, with warfarin being widely used as an anticoagulant to prevent thromboembolism. Antidepressants are typically grouped according to their mechanism of action, which include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), mirtazapine, and bupropion. SSRIs and SNRIs are frequently prescribed to patients taking warfarin who have other comorbidities such as major depression, anxiety, and other psychiatric disorders.

Although there are concerns regarding bleeding risks associated with warfarin and antidepressants, only some antidepressants increase the risk of bleeding when given concurrently with warfarin. Thus, prescribers and pharmacists may see irrelevant warnings because of the lack of distinction across the antidepressants with respect to the risk of bleeding. This artifact provides specific and contextualized alerts to enhance the ability of CDS systems to appropriately deliver pertinent information to the clinician.

## Primary Use Case

This project seeks to provide a necessary bridge between electronic health records and healthcare providers in the clinical decision making process. Providing information to clinicians about drug-drug interaction warnings based on known attributes of the medications involved and patient specific factors is our goal. In essence, we seek to get the right information, at the right time, through the right channel, and the right format to clinicians. The construction of meaningful DDI algorithms will permit healthcare providers, organizations, and systems to provide useful decision support to reduce patient harm due to these drug-drug interactions.

## Proposed Alerting Algorithm

The algorithm first identifies basic concomitant exposures of warfarin and antidepressants. Among these concomitant exposures, the algorithm identifies whether the type of antidepressant is a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). If so, the algorithm then determines whether the patient has one or more risk factors for major bleeding based on other pertinent medical history and ongoing drug exposures. Patients with one or more risk factors for major bleeding yield a Class 1 (Red) alert, while those without additional risk factors result in a Class 2/3 (Yellow) alert.

For antidepressants that are not SSRI’s or SNRI’s, if the type of antidepressant is a mirtazapine, a Class 2/3 (Yellow) alert is fired. Otherwise, if the antidepressant is a tricyclic or bupropion, a Class 4 (Green) alert is fired.

Drug factors involved:

* Warfarin
* SSRI’s and SNRI’s
* Mirtazapine
* Tricyclics
* Bupropion

Risk factors considered for major bleeding:

* History of Gastrointestinal Bleeds
* Older than 64 years of age
* NSAIDs
* Aspirin
* Systemic corticosteroids
* Aldosterone antagonists
* Anti-platelet medications

# Guideline Interpretation and Clinical Decisions

Alert Classifications:

* Class 4: Green: No Special Precautions
  + For Warfarin – Antidepressants rule:
    - Recommendation: No special precautions
    - Rationale: Increased bleeding risk unlikely
* Class 2/3: Yellow: Usually Avoid Combination or Minimize Risk
  + For Warfarin – Antidepressants rule:
    - Recommendation: Assess risk and take action if necessary
    - Rationale: Increased GI and non-GI bleeding risk is possible
* Class 1: Red: Avoid Combination
  + For Warfarin – Antidepressants rule:
    - Recommendation: Use only if benefit outweighs risk
    - Rationale: Increased GI and non-GI bleeding risk is likely

# Artifact Manifest

…

**Table 1: Artifact Manifest**

|  |  |  |
| --- | --- | --- |
| **Filename** | **Purpose** | **Author(s)** |
| [Logic flow diagram](https://ddi-cds.org/wp-content/uploads/2020/02/Warfarin-and-SSRIs-Graph-V8.pdf) | The flow diagram of the decision tree for this algorithm |  |
| [warfarin-antidepressants.drl](https://github.com/rkboyce/iDIA_Rules/blob/ec-sql-modifiedclasses/src/main/resources/rules_progress/warfarin_antidepressants.drl) | Computable Drools code to implement this algorithm’s decision tree |  |
| [Warfarin-Antidepressants CQL](https://github.com/dbmi-pitt/CQL-Testing-Framework/blob/master/pddi-rule-tests/warfarin-antidepressants/warfarin-antidepressants.zip) | Compressed ZIP folder for CQL code written to run over synthetic test cases in the CQL Testing Framework |  |
| [Warfarin value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.8/expansion/Latest) | VSAC value set containing RxCUI’s for warfarin drugs |  |
| [SSRI’s and SNRI’s value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.33/definition) | VSAC value set containing RxCUI’s for SSRI and SNRI drugs |  |
| [Mirtazapine value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.32/definition) | VSAC value set containing RxCUI’s for mirtazapine drugs |  |
| [Tricyclics value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.31/definition) | VSAC value set containing RxCUI’s for tricyclic drugs |  |
| [Bupropion value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.30/definition) | VSAC value set containing RxCUI’s for bupropion drugs |  |
| [History of Gastrointestinal Bleeds value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.53/definition) | VSAC value set containing ICD9CM codes for conditions related to a history of gastrointestinal bleeds |  |
| [NSAID value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.9/expansion/Latest) | VSAC value set containing RxCUI’s for NSAID drugs |  |
| [Aspirin value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.29/definition) | VSAC value set containing RxCUI’s for aspirin drugs |  |
| [Systemic Corticosteroids value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.46/definition) | VSAC value set containing RxCUI’s for systemic corticosteroid drugs |  |
| [Aldosterone Antagonists value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.52/definition) | VSAC value set containing RxCUI’s for aldosterone antagonist drugs |  |
| [Anti-platelet Medications value set](https://vsac.nlm.nih.gov/valueset/2.16.840.1.113762.1.4.1213.50/definition) | VSAC value set containing RxCUI’s for anti-platelet drugs |  |
| [Discussion Forum](https://forums.dikb.org/t/warfarin-antidepressants/233) | Public discussion about the warfarin – antidepressants rule |  |
| [Feedback link](http://utahcop.az1.qualtrics.com/jfe/form/SV_8j1T8SvXGckTqD3) |  |  |

## Artifact Relationship Diagram

# Testing

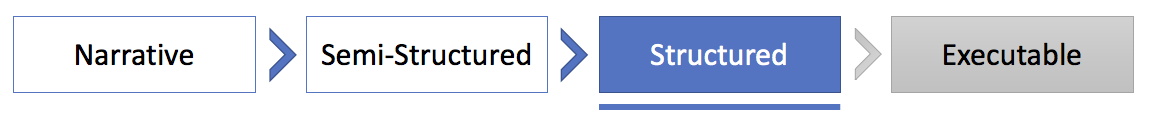
# Implementation Checklist

Boxwala et al.3 developed a multi-layered knowledge representation framework for structuring guideline recommendations as they are transformed into CDS artifacts. The framework defines four “layers” of representation:

1. **Narrative** text created by a guideline or CQM developer (e.g., the recommendation statement described as a sentence).
2. **Semi-structured** text that describes the recommendations for implementation as CDS, often created by clinical subject matter experts. It serves as a common understanding of the clinical intent as the artifact is translated in to a fully structured format by software engineers.
3. **Structured** code that is interpretable by a computer and includes data elements, value sets, and coded logic.
4. **Executable** code that is interpretable by a CDS system at a local level. This code will vary for each site.

This artifact is a **structured** representation of medical knowledge that contains code files that represent the source content (e.g., recommendation statement).

**Figure 2: CDS Artifact Maturity Process**



Prior to incorporating this artifact in a production setting, implementers should consider the following items:

* Analyze the purpose, clinical statement, and use case sections of this document to ensure that your organization understands and agrees with the intended goals of the clinical guideline on which this artifact is based.
* Review the “clinical considerations” section of this document (including the decision log in Appendix B) to ensure that your organization understands and agrees with the decisions made during the process to convert the underlying clinical guideline to a structured, computable CDS artifact.
* Technical staff should read through each of the files in the artifact manifest to understand their respective purposes and how they can be successfully incorporated into a clinical IT system. At the time of publication, many COTS EHR systems are unable to use CQL files natively and require a separate application to convert CQL code such that it can be used in those EHR systems. Implementers should work with vendors of their respective health IT products to understand their readiness to implement CQL code and any potential adverse impacts to existing functionality. In a pilot setting, developers have worked around existing EHR limitations by implementing a web service wrapper around a CQL execution engine. This is a non-trivial amount of work with two primary components:
  + a CQL execution engine with a RESTful web service designed to accept requests for CQL execution and to respond with the calculated results, and
  + modifications to the EHR system such that it will
    - trigger RESTful events to call the CQL execution engine,
    - interpret the response,
    - and reflect the CQL-generated recommendations and suggested actions in the EHR user interface.
* After incorporation into a development environment, the artifact should be exhaustively tested against predefined test cases. Additionally, testing should be conducted to ensure that implementation of the artifact has no adverse effect on the processing efficiency of the health IT system.
* Documentation and training materials for clinical staff should be drafted and distributed. These training materials should include descriptions of modified functionality, directions for interacting with CDS rules (if different than in the current system), and contact information for assistance in the event that functionality does not meet expectations.

# Potential Reuse Scenarios

CQL code within this artifact was developed to enact a particular clinical guideline, but there are portions of the CQL code that are expected to be useful for other purposes.

* The CDS\_Connect\_Commons\_for\_FHIRv102 and FHIRHelpers libraries included in the artifact define commonly used functions in CQL files and are not specific to the Statin Therapy for the Prevention and Treatment of Cardiovascular Disease (CVD) Electronic Clinical Quality Measure (eCQM) artifact. They are expected to be used with any other CQL file that could benefit from those functions.
* Selected code blocks from Statin\_Therapy\_for\_the\_Prevention\_and\_Treatment\_of\_CVD\_eCQM\_Derived\_FHIRv102 could be copied and reused in other CQL files. For example, some have expressed interest in the definition of pregnancy (based on the existence of either a condition code or observation code).

# How Artifact Operates Within CQL

The Statin Therapy for the Prevention and Treatment of Cardiovascular Disease (CVD) Electronic Clinical Quality Measure (eCQM) artifact is composed of several files, but the primary focus of the artifact is the introduction of CQL files that can be used by any healthcare organization to properly identify populations of patients that require a specific message or clinical intervention. CQL is a data standard governed by Health Level 7 (HL7) that is currently a Standard for Trial Use (STU). CQL expresses logic in a human-readable document that is also structured enough for electronic processing of a query. It can be used within both the CDS and CQM domains.

If you would like to learn more about CQL, there are a few resources (care of the [eCQI Resource Center](https://ecqi.healthit.gov/cql)) that you should review:

1. [CQL STU Release 1 at HL7](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=400)
2. [CQL Tools on GitHub](https://github.com/cqframework/clinical_quality_language)
3. [CQL Formatting and Usage Wiki](https://github.com/esacinc/CQL-Formatting-and-Usage-Wiki/wiki)
4. [CQL Online](http://cql-online.esacinc.com/)
5. [CQL Q&As on the eCQI Resource Center](https://ecqi.healthit.gov/cql/CQ-Qs%26As)

# How Artifact Operates Within Drools

A JBoss Drools rule engine (version 6.5.0.Final) uses a custom Java-based controller to load data from an OMOP database. A JDBC driver links the database to the rule engine. From the database, entities for each patients’ relevant diagnoses, drugs, lab measurements, and other risk factors are identified and used in working memory. The rules written use this data to identify patients that satisfy criteria specified for each decision portrayed in the DDI decision tree. The rule engine iterates on a day-by-day basis throughout a specified study period and outputs alerts and relevant factors that occur on a specific day.

The Drools rule engine is available as a [GitHub project](https://github.com/rkboyce/iDIA_Rules/tree/ec-sql-modifiedclasses). This project includes a [Docker container](https://hub.docker.com/r/ddicds/idia_rules) which can be used to virtualize the rule engine so that the audience can customize their own use case by choosing if they want to run one specific rule of interest, or if they have their own OMOP database connection that they wish to input to read data from.

After pulling the docker container using the command docker pull ddicds/idia\_rules, The following command can be used to run the docker container over the default synthetic population:

docker run -v ~/simulated-run/:/app/simulated-run -it --rm ddicds/idia\_rules:localdb simulated

To run the rules over a custom database connection and/or specify a particular rule to isolate in the run, the following additional arguments can be added to the above command:

connectionURL={URL} ruleFolder={rule options listed below} schema={schema} user={user} password={password} sslmode=require

The sslmode argument is optional and its presence is dependent on the specific configuration of the database that the user wishes to connect to.

By default, all rules are run, but to specify individual rules, strings that can be passed into the ruleFolder argument include:

* rules\_acei\_arb\_ksparing\_diuretics
* rules\_ceftriaxone\_calcium
* rules\_citalopram\_QT\_agents
* rules\_clonidine\_betablockers
* rules\_epi\_betablockers
* rules\_fluconazole\_opioids
* rules\_immunosuppressants\_fluconazole
* rules\_k\_ksparing\_diuretics
* rules\_warfarin\_antidepressants
* rules\_warfarin\_nsaids
* rules\_warfarin\_salicylates

# Running the Rule in the CQL Testing Framework

The CQL project, its dependencies, and YAML test cases for all of the rule’s leaf nodes are available in a [ZIP format](https://github.com/dbmi-pitt/CQL-Testing-Framework/blob/master/pddi-rule-tests/warfarin-antidepressants/warfarin-antidepressants.zip) that should include a folder with all required components for the rule. This folder alone should be sufficient to run the rule over the included YAML test cases that can be found in the “tests” subdirectory. Within this folder, the “cql” subdirectory should include the rule-specific CQL script alongside its JSON translation, as well as additional pairs of such files that serve as dependencies for the rule-specific CQL.

A “.vscache” folder should be included in the ZIP file so that the necessary value set definitions can be used without requiring the user to set UMLS VSAC credentials. The script library in the “node\_modules” folder is managed by Node.js and the Node Package Manager (NPM). With these dependencies included, to run the CQL rule, the user should be able to simply run “npm test” in the command line from the base directory of the unzipped folder.

By default, the included YAML test cases should all yield successful tests, and the output of the “npm test” command should indicate the number of passing tests.

The [README](https://github.com/dbmi-pitt/CQL-Testing-Framework/blob/master/README.md) for the overall CQL Testing Framework project provides additional details about developing and using this system. For information about writing YAML test cases to further explore how the CQL script can handle other scenarios outside of the included test cases, this [README](https://github.com/dbmi-pitt/CQL-Testing-Framework/blob/master/CREATING-TEST-CASES.md) should describe how to create YAML files.

**Appendix A: Test Data**

In conjunction with a custom Node.js testing framework, the following data tables were used to test the artifact:

**Table 2: Class 4 (Green) Alert Basic Tests**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient ID** | **Age** | **Rule Branch** | **Warfarin** | **Antidepressant** | **Bleeding Risk Factor** | **RESULT: Recommendation** | **RESULT: Rationale** |
| 1573 | 48 | Warfarin / Tricyclic or Bupropion | Warfarin Sodium 10 MG Oral Tablet | Bupropion 50 MG Extended Release Tablet | N/A | No special precautions | Increased bleeding risk unlikely |

**Table 3: Class 2/3 (Yellow) Alert Basic Tests**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient ID** | **Age** | **Rule Branch** | **Warfarin** | **Antidepressant** | **Bleeding Risk Factor** | **RESULT: Recommendation** | **RESULT: Rationale** |
| 1572 | 38 | Warfarin / Mirtazapine | Warfarin Sodium 10 MG Oral Tablet | Mirtazapine 45 MG Disintegrating Oral Tablet | N/A | Assess risk and take action if necessary | Increased GI and non-GI bleeding risk is possible |
| 1525 | 68 | Warfarin / SSRI or SNRI with no major bleeding risk factors | Warfarin Sodium 10 MG Oral Tablet | Escitalopram 20 MG Oral Tablet | None | Assess risk and take action if necessary | Increased GI and non-GI bleeding risk is possible |
| 1529 | 28 | Warfarin / SSRI or SNRI with no major bleeding risk factors | Warfarin Sodium 10 MG Oral Tablet | Escitalopram 20 MG Oral Tablet | None | Assess risk and take action if necessary | Increased GI and non-GI bleeding risk is possible |

**Table 4: Class 2/3 (Red) Alert Basic Tests**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient ID** | **Age** | **Rule Branch** | **Warfarin** | **Antidepressant** | **Bleeding Risk Factor** | **RESULT: Recommendation** | **RESULT: Rationale** |
| 1526 | 33 | Warfarin / SSRI or SNRI with major bleeding risk factors | Warfarin Sodium 10 MG Oral Tablet | Escitalopram 20 MG Oral Tablet | Systemic Corticosteroid = Prednisone 5 MG Oral Tablet | Use only if benefit outweighs risk | Increased GI and non-GI bleeding risk is likely |
| 1527 | 16 | Warfarin / SSRI or SNRI with major bleeding risk factors | Warfarin Sodium 10 MG Oral Tablet | Escitalopram 20 MG Oral Tablet | Aldosterone Antagonist = Spironolactone 100 MG Oral Tablet | Use only if benefit outweighs risk | Increased GI and non-GI bleeding risk is likely |
| 1528 | 18 | Warfarin / SSRI or SNRI with major bleeding risk factors | Warfarin Sodium 10 MG Oral Tablet | Escitalopram 20 MG Oral Tablet | History of GI Bleeds = Acute peptic ulcer with hemorrhage | Use only if benefit outweighs risk | Increased GI and non-GI bleeding risk is likely |

**Appendix B: Decision Log**

The decision log was generated per procedures published by Tso et al.,4 which incorporates and extends steps that Shiffman et al.5 outlined for translating clinical practice guidelines to CDS. Brief descriptions of the steps in this process are included in the following table:

**Table 5: Definitions of Shiffman's Steps**

|  |  |
| --- | --- |
| **Decision Category** | **Definition** |
| **Select Guidelines** | Choosing specific guidelines and specific recommendations within the selected guidelines to be implemented |
| **Markup** | Identifying and tagging guideline knowledge components relevant to operationalization |
| **Atomize** | The process of extracting and refining single concepts from the narrative text recommendations |
| **Deabstract** | The process of adjusting the level of generality at which a decision variable or action is described to permit operationalization |
| **Disambiguate** | The process of establishing a single semantic interpretation for a recommendation statement |
| **Build Executable Statements** | Arranging the atomized, de-abstracted, and disambiguated decision variables and actions into logical statements that can be translated readily into computable statements |
| **Verify Completeness** | The process of making sure that each recommendation provides guidance in all situations that a clinician is likely to face |
| **Add Explanation** | A facility to describe the reasoning behind recommendations |
| **Identify Origin** | Identifying a source or origin in the clinical environment for each decision variable |
| **Insert Recommendations** | Identifying an insertion point in the care process for each recommended action |
| **Define Action Type** | Categorizing guideline-recommended activities per predefined action types |
| **Define Associated Beneficial Services** | Linking action types to associated beneficial services that offer design patterns for facilitating clinical care |
| **Design User Interface** | Selecting and grouping user interface elements to best deliver CDS output |

or who receive an order (prescription) for statin therapy at any point during the measurement period.

**Decision Logs**

**Table 6: Decisions Based on "Atomized" Components of the Population Statements**

|  |  |  |
| --- | --- | --- |
| **Presence in Statement** | **"Atomized" Word or Phrase** | **Interpretation or Rationale** |
|  |  |  |
|  |  |  |

Several decisions were made outside the scope of the atomized words and phrases in the recommendation statements. These additional decisions were made based on the best available clinical knowledge and were encountered at various stages in the artifact development process.

**Table 7: Additional Decisions**

|  |  |  |
| --- | --- | --- |
| **Decision Category** | **Concept** | **Rationale** |
| Select guidelines |  |  |
| Disambiguate |  |  |
| Implementation guidance |  |  |
| Deabstract |  |  |
| **Logic constraints to ensure clinical relevance:** | | |
| Add explanation |  |  |
| Add explanation |  |  |
| Deabstract |  |  |

**Appendix C: Acronyms**

|  |  |
| --- | --- |
| **ACA** | Affordable Care Act |
| **AHRQ** | Agency for Healthcare Research and Quality |
| **CAMH** | CMS Alliance to Modernize Healthcare |
| **CDS** | Clinical Decision Support |
| **CMS** | Centers for Medicare & Medicaid Services |
| **COTS** | Commercial Off-the-Shelf |
| **CQL** | Clinical Quality Language |
| **CQM** | Clinical Quality Measurement |
| **CVD** | Cardiovascular Disease |
| **eCQI** | Electronic Clinical Quality Information |
| **EHR** | Electronic Health Record |
| **FAR** | Federal Acquisition Regulation |
| **FFRDC** | Federally Funded Research and Development Center |
| **FHIR** | Fast Healthcare Interoperability Resources |
| **HDL** | High-Density Lipoprotein |
| **HHS** | Department of Health and Human Services |
| **HIT** | Health Information Technology |
| **HL7** | Health Level 7 |
| **IT** | Information Technology |
| **LDL** | Low-Density Lipoprotein |
| **ONC** | Office of the National Coordinator for Health Information Technology |
| **PCOR** | Patient-Centered Outcomes Research |
| **PCORI** | Patient-Centered Outcomes Research Institute |
| **RSAs** | Recommendations and Suggested Actions |
| **USPSTF** | U.S. Preventive Services Task Force |

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