Reviewer's report

Title: Criteria for assessing High-priority Drug-Drug Interactions for Clinical Decision Support in Electronic Health Records

Version: 2 Date: 12 February 2013

Reviewer: Marine Andersson

Reviewer's report:

In the present study the investigators have made a systematic literature search to identify criteria for drug-drug interactions that should be prioritized for inclusion in electronic health records. An expert panel has used this information for basis for writing a modified and more specific list of criteria. The topic is of great interest since there is a huge problem with non-optimized drug interaction warning systems causing alert fatigue due to high rate or irrelevant warnings.

Discretionary Revisions
1. How was the literature search performed? Which exact Mesh terms/ Emtree words were used? In figure 1 you specify all terms used but it is not clear if some of them were MeSH terms/Emtree terms or not.

Minor Essential Revisions
2. Page 11, correct the spelling of aripiprazole (line 5, 8, 10, 11)
3. Page 18, line 14, correct the spelling of itraconazole

Major Compulsory Revisions
4. How many criteria were identified by the literature search and how many of them were disregarded? Please comment on this in the manuscript.

5. The aim of the study, according to the abstract, is to identify a set of criteria for assessing the severity of DDIs. The criteria presented in the results are, to my opinion, not criteria for assessing the severity of DDIs but rather important criteria for how to choose which interactions to include in an EHR. Please specify what are the specific purpose of the study. Also add in the discussion how these criteria should be used to improve drug-drug interaction warnings in electronic health care records.

6. Some of the criteria specifically regarding clinical implications and patients characteristics are interesting and valuable but maybe not yet feasible to use. For example, scientific evidence on how to handle interactions and how they are altered by patient characteristics is unfortunately almost always lacking. This would make these criteria difficult to follow today but hopefully there will be more information about this in 5-10 years. Please comment on this in the manuscript.

7. The handling of the interaction between aripiprazole and amiodarone is
discussed on page 11. One of the suggestions is to replace amiodarone by a calcium channel blocker that do not inhibit the metabolism of aripiprazole (CYP3A4 mediated). Amiodarone is used for cardiac arrhythmia and replacing it by a calcium channel blocker is usually not feasible. Furthermore amiodarone has a long half life and the interaction may persist months after withdrawal. Monitoring of the plasma concentration of aripiprazole could also be recommended when used in combination with amiodarone.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests