

1. Publishable summary



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Before launching a new drug to the market, it is tested on a few thousands of people, but adverse drug reactions (ADRs) may not be detected until many more patients have used the drug. Once the drug is on the market, clinicians are responsible for recognizing and reporting suspected side effects, which are collected in so-called spontaneous reporting systems. However, a number of recent, highly publicized drug safety issues showed that adverse effects of drugs may be detected too late, when millions of patients have already been exposed.

In EU-ADR, an alternative approach towards the detection of ADRs will be developed to overcome the shortcomings of spontaneous reporting databases and to provide a solid basis for large-scale monitoring of drug safety. In EU-ADR a systematic calculation of the occurrence of specific diseases (potential ADRs) during drug use will be based on data available in electronic patient records, with special attention to patient groups that are not routinely involved in clinical trials, for ethical or practical reasons. Once generated, the signals will be substantiated by applying causality criteria (biological plausibility, known reactions). The purpose of this substantiation process is to place the signals in the context of current biomedical knowledge which might explain the signal.

As outlined in the original proposal, the activities during the first year of EU-ADR reflect the different steps that must be set to reach the project goals.

The *first* step is the identification of events that we will monitor in EU-ADR. The different databases participating in EU-ADR all have their own coding schemes. It is not feasible to map all entities in these coding schemes on each other. Instead, we wanted to focus on a limited set of events that carry the major burden of the ADRs. A first major result of EU-ADR was the definition of such a list of high-impact events to monitor, based on the currently available literature. The paper documenting that analysis has been submitted for publication in a journal. In addition, based on literature analysis, test sets of known drug-adverse event associations were defined (e.g., upper gastrointestinal bleeding is a known side effect of non-steroidal anti-inflammatory drugs). These test sets will be used to assess the performance of the systems and procedures developed in EU-ADR.

The *second* step is mapping of the different coding schemes used by the databases onto a common set of selected events. Using the Unified Medical Language System (UMLS) as a pivot, terms have been selected that link codes from the local coding scheme (e.g., Read codes) to the event of interest. The methods and procedures in this activity have been defined and were first tested on the upper gastrointestinal bleeding event.

The *third* step is the actual retrieval of data in the participating databases, followed by analysis, aggregation, and finally pooling of results. For the first event, upper gastrointestinal bleeding, the process has been completed. For the retrieval and aggregation, a software package, called Jerboa, has been developed. A journal paper

documenting the first experiences with Jerboa and upper gastrointestinal bleeding is in preparation.

The *fourth* step is to “rediscover” known associations, using the test sets defined in the first step. The first association that we “rediscovered” is the relation between NSAIDs and upper gastrointestinal bleeding. To allow comparison of the different classifications of medications across the various databases, we have standardized on the ATC classification for drugs. We could demonstrate that NSAIDs have a significantly increased risk for upper gastrointestinal bleeding. We are preparing a journal paper that documents this confirmation of a known side effect throughout different European databases.

Parallel to these activities, work has started on the substantiation process, which places the signals in the context of current biomedical knowledge in order to explain the signal. These activities have progressed significantly. In the upcoming year, this substantiation process will be further developed.

Finally, the EU-ADR project has received a significant amount of attention as also witnessed by the dissemination activities. During the first year, we have engaged in initial conversations with related projects (both European and US) to explore the potential of collaboration. Although interests in collaboration were expressed, these have not yet been translated into formal collaborations.