MAED Service: FDA-Developed Tool for Clinical AE Data Signal Detection

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ABSTRACT

Background: MAED was originally developed in 2009 using a Regulatory Science and Research (RSR) grant. It has been published in a clinical trial setting for use as a prototype since that time. In addition, there are some levels of support from various CDER and OCS groups for new enhancements.

The MAED Service is an FDA-developed tool that was developed for FDA medical and statistical evaluation of adverse event (AE) data coded to the Medical Dictionary for Regulatory Activities (MedDRA). MAED stands for MedDRA-based Adverse Event Diagnosis. The MAED Service allows reviewers to perform important safety signal detection assessments. MAED is currently in pre-production in CDER and has proven to be a powerful signal detection tool.

METHODS

MAED is an application for analysis of adverse events (AEs) in clinical trial data and AE databases. It is assumed that AEs are coded using MedDRA, version 6.0 or later (currently up to 15.0). Either preferred terms (PT) or PT codes can be used for analysis. Input data files are assumed to be either SAS datasets or SAS zip files.

MAED rapidly builds the following for all MedDRA terms (Complete Hierarchy) and all Standardized MedDRA Queries (SMQ):

- Basic statistics including: event counts, counts of subjects with events; calculated proportion of subjects with events
- Multiple Risk Estimators including:
  - Odds ratio (OR) with 95% confidence interval – exact
  - Risk difference (RD) with 95% confidence interval – asymptotic
  - Relative risk (RR) with 95% confidence interval
  - P-value – Fischer’s Exact Test (2-sided).

All statistics are calculated from the 2 × 2 table formed by number of subjects with events and total number of subjects in the reference and comparison groups.

CONCLUSIONS

MAED is currently in pre-production in CDER and has proven to be a powerful signal detection tool. The MAED service can be used with both standard and non-standard data. However, it requires users to either use SAS dat format or Excel format. Reviewing the MedDRA version coded in data is extremely important to avoid any unwanted results or terms dropped from analysis.

As a result, the MAED Service was developed as a tool to allow reviewers to do their own AE safety assessments of products by being able to look at treatment group comparison of adverse events by analyzing at different levels of the MedDRA hierarchy. The tool also provides analysis to all SMQs with the MedDRA version used as the reference. The tool helps reviewers identify potential safety signals for further exploration and aids in identifying safety signals that may have been split amongst different preferred terms by examining SMQs.

In addition to Standard MedDRA Query, the reviewers can create their own custom MedDRA Query and analyzing them based on their clinical judgments.

MAED is currently in pre-production with limited FDA reviewers who can access and utilize it. There are some enhancements under exploration for MAED Service. FDA reviewers are taught to interpret MAED with caution. Its intended function is to support exploration of potential safety signals only and must not necessarily provide definitive findings. The P-value/confidence intervals are calculated, however, the interpretation of tests such as p-values and confidence intervals should be approached with extreme caution due to potential issues with multiplicity, misclassification, ascertainment, testing, and other possible biases.