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

Xin (Joy) Li; Chuck Cooper; Zhongjun Luo
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ABSTRACT

Background:
MAED was originally developed in 2009 using a Regulatory Science and Research (RSR) grant. It has been available to a limited number of users as a prototype since that time, in addition, there are some level of supported with training, customer service, and new software enhancement releases.

The MAED Service is an SAS®-based tool that was developed for FDA medical and statistical reviewers of adverse event (AE) data coded to the Medical Dictionary of Regulatory Activities (MedDRA). MAED stands for MedDRA-based Adverse Event Diagnostics. The MAED Service allows reviewers to perform important safety signal detection assessments including: AE analysis by each level of the MedDRA hierarchy, and SMQ analyses. All SMQs, including broad, narrow, algorithmic, parent and child are derived using each patient's AE data. For each level of the MedDRA hierarchy and each SMQ class (narrow- or broad-scope), terms are displayed in a summary report that uses several sortable risk estimators that display degree of disparity between comparison groups (e.g. test drug vs. placebo). So the first term displayed in the MAED Service report represents the term, for the given level, with the largest degree of disparity, according to the reviewer selected risk estimator, between the groups being compared. This approach, for the first time ever, provides reviewers with the ability to effectively utilize SMQs and MedDRA hierarchy analyses as an important safety signal detection strategy. Reviewers are then able to use their clinical and reviewer judgment to prioritize and explore potential signals that might be important to determine if those signals are meaningful.

INTRODUCTION

MAED (MedDRA Adverse Event Diagnostics) is a web-based application with SAS running behind a Java GUI which was developed within by FDA reviewers to aid in safety signal detection. It provides reviewers with an initial assessment of adverse event data for reviewers who can then more judiciously explore possible safety issues. Reviewers use their clinical and reviewer judgment to prioritize and explore potential signals that might be important to determine if those signals are meaningful.

MAED analyses are possible because of the use of a standard medical terminology (MedDRA). MedDRA (the Medical Dictionary for Regulatory Activities) is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (e.g., medical devices and vaccines). Coding these data to a standard set of MedDRA terms (Preferred Terms) allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products.

The MedDRA terminology has been recommended by FDA/CDER for use to report averse event data from clinical trials and for post-marketing reports and pharmacovigilance. One useful feature of MedDRA is its hierarchical structure which allows uses to analyze broader grouping terms which coalesce similar, related terms from the level beneath. This aids in signal detection because a single toxicity that has been coded to multiple MedDRA terms may be easier to identify when analysis uses the grouping terms (High Level Term, High Level Group Term, and System Organ Class). MeDRA also includes Standardized MedDRA Queries (SMQs). These SMQs represent custom queries of the MedDRA Preferred Terms in which CIOMS expert working groups have identified collections, combinations, or algorithms of various adverse event preferred terms that are potentially consistent with a variety of over 200 toxicities.

FDA reviewers are taught that proper adverse event analysis strategies designed to identify potential safety signals include: analysis on all levels of the MedDRA hierarchy; analysis using SMQs. These techniques have been shown to be helpful in dealing with MedDRA granularity, in which multiple subjects with the same toxicity may have had their adverse events coded to a variety of similar, but different Preferred Terms.

METHODS

MAED is an application for analysis of adverse events (AEs) in clinical trials 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 (PTs) or PT codes can be used for analysis. Input data files are assumed to be either SAS datasets or SAS xpt files.

MAED rapidly batch produces 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 – Fisher'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.

MAED Process And Results

Through web browser, reviewers can access MAED via their FDA computer. There are only few steps with some information about data. See screens for steps to run MAED services in the "MAED: Step by Step" section

MAED produces a summary report in excel with multiple spreadsheets. Each sheet presents comparative analysis for all MedDRA levels of adverse events, including SOC, HLGT, HLT, PT as well as the broad SMQ, narrow SMQ, and algorithmic SMQ. Custom queries can also be used. Also there are 2 augmented SAS datasets produced for MedDRA Hierarchy and SMQs coding. These datasets support further analysis and exploration of potential safety signals.

CONCLUSIONS

MAED is currently in pre-production in CDER and has proven to be a powerful signal detection tool.

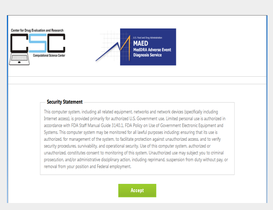
The MAED service can be used with both standard and non-standard data. But it would require data to be either sas7bdat or xpt format. Knowing the MedDRA version coded in data is extremely important to avoid any unmatched prefer terms dropped from anaylsis.

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 comparisons of adverse by analyzing at different levels of the MedDRA hierarchy. The tool also provides analysis to all SMQs with the most current MedDRA versions as needed. This tool helps Reviewers identify potential safety signals for further exploration and aids in identifying safety signals that may have been split amongst many preferred terms by searching SMQs.

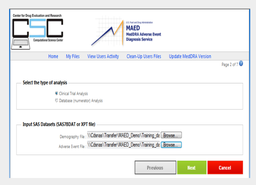
In addition to Standard MedDRA Query, the reviewers can create their own custom MedDRA Query and analyzing them based on their clinical judgments.

MAED is currently in pre-production with limited FDA reviewers who can access and utilize it. There are some enhancements under exploratoration 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 not to 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.

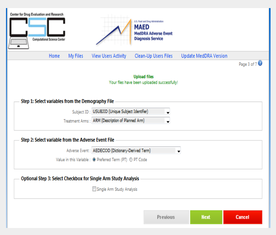
MAED: Step by Step



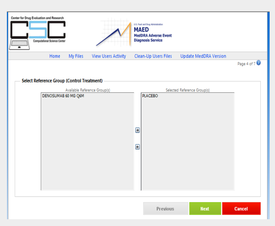
1. Intro Information



2. Data is Loaded (sas7bdat or .xpt)

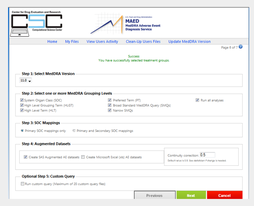


3. Relevant Variables are selected

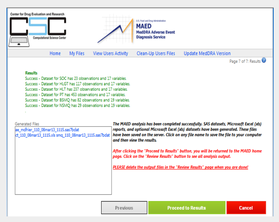


4. Comparator is identified

5. Study drug is identified and event plus subject filtering occurs



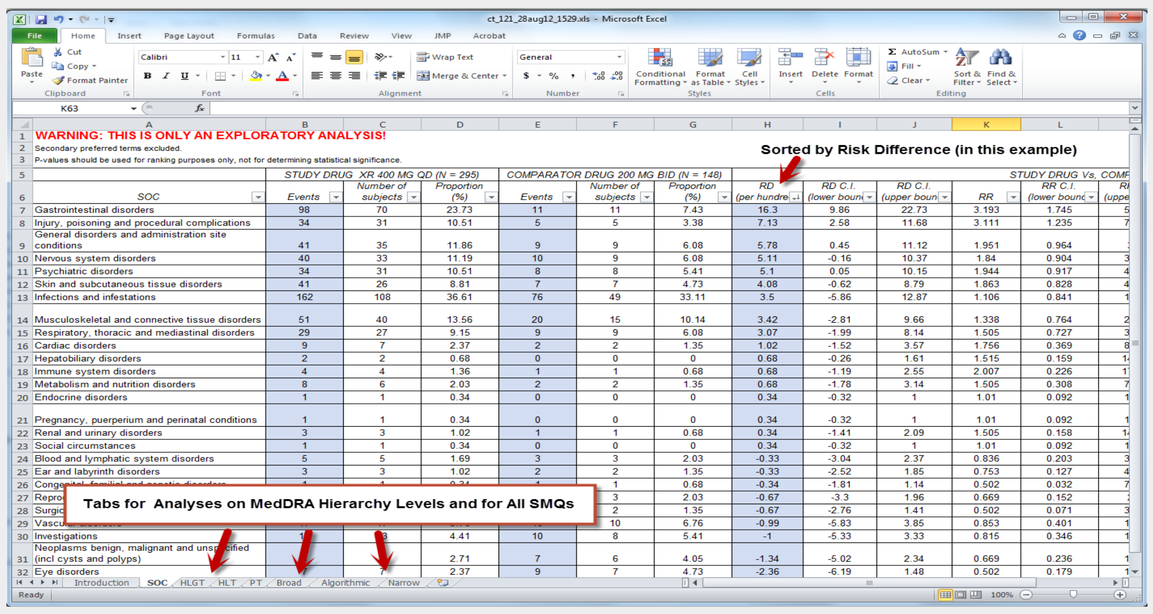
6.
- MedDRA version is selected
- Desired hierarchy and SMQ analyses selected
- Continuity correction selected



7. Output excel workbook and sas datasets are made available

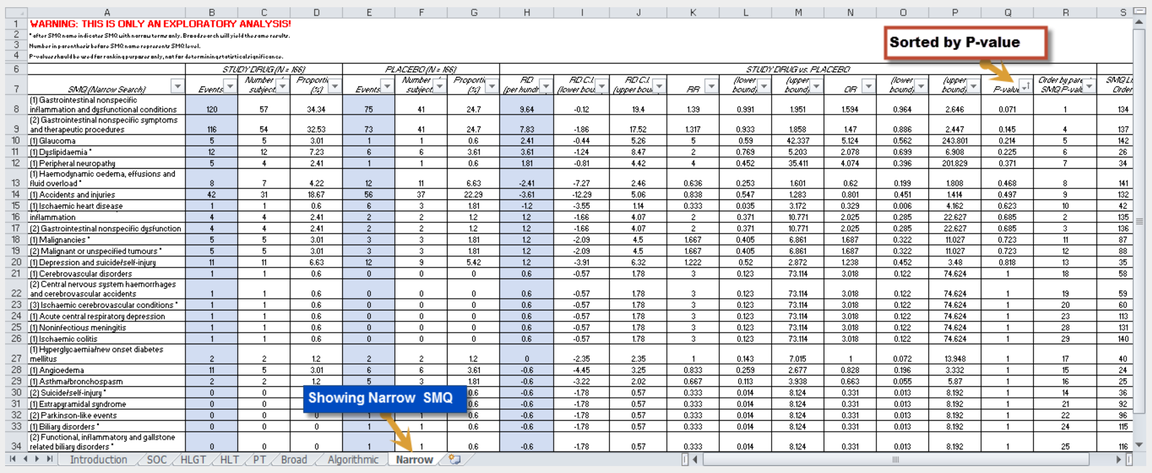
Results of MAED Analysis

Table 1: AE MedDRA Hierarchy summary at SOC level



SOC	STUDY DRUG XR 400 MG QD (N = 295) Events	Number of subjects	Proportion (%)	COMPARATOR DRUG 200 MG BID (N = 148) Events	Number of subjects	Proportion (%)	STUDY DRUG Vs. COMP RD (per hundr	RD C.I. (lower boun	RD C.I. (upper boun	RR	RR C.I. (lower bound	RI (uppe
Gastrointestinal disorders	98	70	23.73	11	11	7.43	16.3	9.86	22.73	3.193	1.745	5
Injury, poisoning and procedural complications	34	31	10.51	5	5	3.38	7.13	2.58	11.68	3.111	1.235	7
General disorders and administration site conditions	41	35	11.86	9	9	6.08	5.78	0.45	11.12	1.951	0.964	
Nervous system disorders	40	33	11.19	10	9	6.08	5.11	-0.16	10.37	1.84	0.904	3
Psychiatric disorders	34	31	10.51	8	8	5.41	5.1	0.05	10.15	1.944	0.917	4
Skin and subcutaneous tissue disorders	41	26	8.81	7	7	4.73	4.08	-0.62	8.79	1.863	0.828	4
Infections and infestations	162	108	36.61	76	49	33.11	3.5	-5.86	12.87	1.106	0.841	1
Musculoskeletal and connective tissue disorders	51	40	13.56	20	15	10.14	3.42	-2.81	9.66	1.338	0.764	2
Respiratory, thoracic and mediastinal disorders	29	27	9.15	9	9	6.08	3.07	-1.99	8.14	1.505	0.727	3
Cardiac disorders	9	7	2.37	2	2	1.35	1.02	-1.52	3.57	1.756	0.369	8
Hepatobiliary disorders	2	2	0.68	0	0	0	0.68	-0.26	1.61	1.515	0.159	1
Immune system disorders	4	4	1.36	1	1	0.68	0.68	-1.19	2.55	2.007	0.226	1
Metabolism and nutrition disorders	8	6	2.03	2	2	1.35	0.68	-1.78	3.14	1.505	0.308	7
Endocrine disorders	1	1	0.34	0	0	0	0.34	-0.32	1	1.01	0.092	1
Pregnancy, puerperium and perinatal conditions	1	1	0.34	0	0	0	0.34	-0.32	1	1.01	0.092	1
Renal and urinary disorders	3	3	1.02	1	1	0.68	0.34	-1.41	2.09	1.505	0.158	1
Social circumstances	1	1	0.34	0	0	0	0.34	-0.32	1	1.01	0.092	1
Blood and lymphatic system disorders	5	5	1.69	3	3	2.03	-0.33	-3.04	2.37	0.836	0.203	3
Ear and labyrinth disorders	3	3	1.02	2	2	1.35	-0.33	-2.52	1.85	0.753	0.127	4
Congenital, familial and genetic disorders	1	1	0.34	1	1	0.68	-0.34	-1.81	1.14	0.502	0.032	7
Repro				3	3	2.03	-0.67	-3.3	1.96	0.669	0.152	
Surgic				3	2	1.35	-0.67	-2.76	1.41	0.502	0.071	3
Vascu				10	10	6.76	-0.99	-5.83	3.85	0.853	0.401	1
Investigations	7	6	4.41	10	8	5.41	-1	-5.33	3.33	0.815	0.346	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	4	2.71	7	6	4.05	-1.34	-5.02	2.34	0.669	0.236	1
Eye disorders	4	4	2.37	9	7	4.73	-2.36	-6.19	1.48	0.502	0.179	1

Table 2: AE MedDRA SMQs summary at narrow search



SMQ (Narrow Search)	STUDY DRUG (N = 166) Events	Number subject	Proporti (%)	PLACEBO (N = 166) Events	Number subject	Proporti (%)	STUDY DRUG vs. PLACEBO RD (per hundr	RD C.I. (lower bou	RD C.I. (upper bou	RR	RR C.I. (lower bound	RR C.I. (upper bound	OR	OR C.I. (lower bound	OR C.I. (upper bound	P-value	Order by narr SMQ P-valu	SMQ Lo Order
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	120	57	34.34	75	41	24.7	9.64	-0.12	19.4	1.39	0.991	1.951	1.594	0.964	2.646	0.071	1	134
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	116	54	32.53	73	41	24.7	7.83	-1.86	17.52	1.317	0.933	1.858	1.47	0.886	2.447	0.145	4	137
(1) Glaucoma	5	5	3.01	1	1	0.6	2.41	-0.44	5.26	5	0.59	42.337	5.124	0.562	243.801	0.214	5	142
(1) Dyslipidaemia *	12	12	7.23	6	6	3.61	3.61	-1.24	8.47	2	0.769	5.203	2.078	0.699	6.908	0.225	6	26
(1) Peripheral neuropathy	5	4	2.41	1	1	0.6	1.81	-0.81	4.42	4	0.452	35.411	4.074	0.396	201.829	0.371	7	34
(1) Haemodynamic oedema, effusions and fluid overload *	8	7	4.22	12	11	6.63	-2.41	-7.27	2.46	0.636	0.253	1.601	0.62	0.199	1.808	0.468	8	141
(1) Accidents and injuries	42	31	18.67	56	37	22.29	-3.61	-12.29	5.06	0.838	0.547	1.283	0.801	0.451	1.414	0.497	9	132
(1) Ischaemic heart disease	1	1	0.6	6	3	1.81	-1.2	-3.55	1.14	0.333	0.035	3.172	0.329	0.006	4.162	0.623	10	42
inflammation	4	4	2.41	2	2	1.2	1.2	-1.66	4.07	2	0.371	10.771	2.025	0.285	22.627	0.685	2	135
(2) Gastrointestinal nonspecific dysfunction	4	4	2.41	2	2	1.2	1.2	-1.66	4.07	2	0.371	10.771	2.025	0.285	22.627	0.685	3	136
(1) Malignancies *	5	5	3.01	3	3	1.81	1.2	-2.09	4.5	1.667	0.405	6.861	1.687	0.322	11.027	0.723	11	87
(2) Malignant or unspecified tumours *	5	5	3.01	3	3	1.81	1.2	-2.09	4.5	1.667	0.405	6.861	1.687	0.322	11.027	0.723	12	88
(1) Depression and suicide/self-injury	11	11	6.63	12	9	5.42	1.2	-3.91	6.32	1.222	0.52	2.872	1.238	0.452	3.48	0.818	13	35
(1) Cerebrovascular disorders	1	1	0.6	0	0	0	0.6	-0.57	1.78	3	0.123	73.114	3.018	0.122	74.624	1	18	58
(2) Central nervous system haemorrhages and cerebrovascular accidents	1	1	0.6	0	0	0	0.6	-0.57	1.78	3	0.123	73.114	3.018	0.122	74.624	1	19	59
(3) Ischaemic cerebrovascular conditions *	1	1	0.6	0	0	0	0.6	-0.57	1.78	3	0.123	73.114	3.018	0.122	74.624	1	20	60
(1) Acute central respiratory depression	1	1	0.6	0	0	0	0.6	-0.57	1.78	3	0.123	73.114	3.018	0.122	74.624	1	23	113
(1) Noninfectious meningitis	1	1	0.6	0	0	0	0.6	-0.57	1.78	3	0.123	73.114	3.018	0.122	74.624	1	28	131
(1) Ischaemic colitis	1	1	0.6	0	0	0	0.6	-0.57	1.78	3	0.123	73.114	3.018	0.122	74.624	1	29	140
(1) Hyperglycaemia/new onset diabetes mellitus	2	2	1.2	2	2	1.2	0	-2.35	2.35	1	0.143	7.015	1	0.072	13.948	1	17	40
(1) Angioedema	11	5	3.01	6	6	3.61	-0.6	-4.45	3.25	0.833	0.259	2.677	0.828	0.196	3.332	1	15	24
(1) Asthma/bronchospasm	2	2	1.2	5	3	1.81	-0.6	-3.22	2.02	0.667	0.113	3.938	0.663	0.055	5.87	1	16	25
(2) Suicide/self-injury *	0	0	0	1	1	0.6	-0.6	-1.78	0.57	0.333	0.014	8.124	0.331	0.013	8.192	1	14	36
(1) Extrapyramidal syndrome	0	0	0	1	1	0.6	-0.6	-1.78	0.57	0.333	0.014	8.124	0.331	0.013	8.192	1	21	92
(2) Parkinson-like events	0	0	0	1	1	0.6	-0.6	-1.78	0.57	0.333	0.014	8.124	0.331	0.013	8.192	1	22	96
(1) Biliary disorders *	0	0	0	1	1	0.6	-0.6	-1.78	0.57	0.333	0.014	8.124	0.331	0.013	8.192	1	24	115
(2) Functional, inflammatory and gallstone related biliary disorders *	0	0	0	1	1	0.6	-0.6	-1.78	0.57	0.333	0.014	8.124	0.331	0.013	8.192	1	25	116

CONTACT INFORMATION

Name: Xin (Joy) Li, MS
At FDA/CDER/OTS/OCS.
Work Phone: 301.796.0168
E-mail: joy.li@fda.hhs.gov

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