



MAED Tool: FDA-Developed Tool for Adverse Event Data Signal Detection in Clinical Safety Analysis

Joy Li; Bobbie Witczak; Christine Wang; Eileen Navarro
OCS, OTS, CDER, FDA



Background and Overview

MAED, one of the earliest tools developed by the Computational Science Center, is a web-based SAS application running behind a Java GUI for analysis of adverse events (AEs). MAED stands for MedDRA-based Adverse Event Diagnostics. Medical and statistical reviewers use MAED as an aide in safety signal detection, using adverse event (AE) data coded to the Medical Dictionary of Regulatory Activities (MedDRA). It is assumed that AEs are coded using MedDRA version 6.0 or later. Either preferred terms (PTs) or prefer term codes can be used for analysis.

Safety signal detection assessments include assessment of 1) individual reported AE terms (by level of the MedDRA hierarchy and 2) by AE concepts based on clustered terms, also known as standard MedDRA queries (SMQ) (See Table 1). Analyses by level of the MedDRA hierarchy or SMQ class (narrow-, broad-scope, or algorithmic) are summarized in a of report of frequency and risk estimators between comparison groups (e.g. test drug vs. placebo). MAED Tool is based on the basic statistics with Multiple Risk Estimators including: Odds ratio (OR), Risk difference (RD), Relative risk (RR), *P*-value for all MedDRA terms (complete hierarchy) and all levels of SMQ.

This report provides reviewers with automated reports that can be further explored in the safety review.

Exploration of events at different levels of the MedDRA hierarchy and using various SMQs classes across treatment arms helps reviewers identify potential safety signals for further exploration. Assessing individual terms in parallel with SMQs enables reviewers to identify safety signals that may be missed if terms are lumped or split amongst many preferred terms.

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

WARNING: THIS IS ONLY AN EXPLORATORY ANALYSIS!

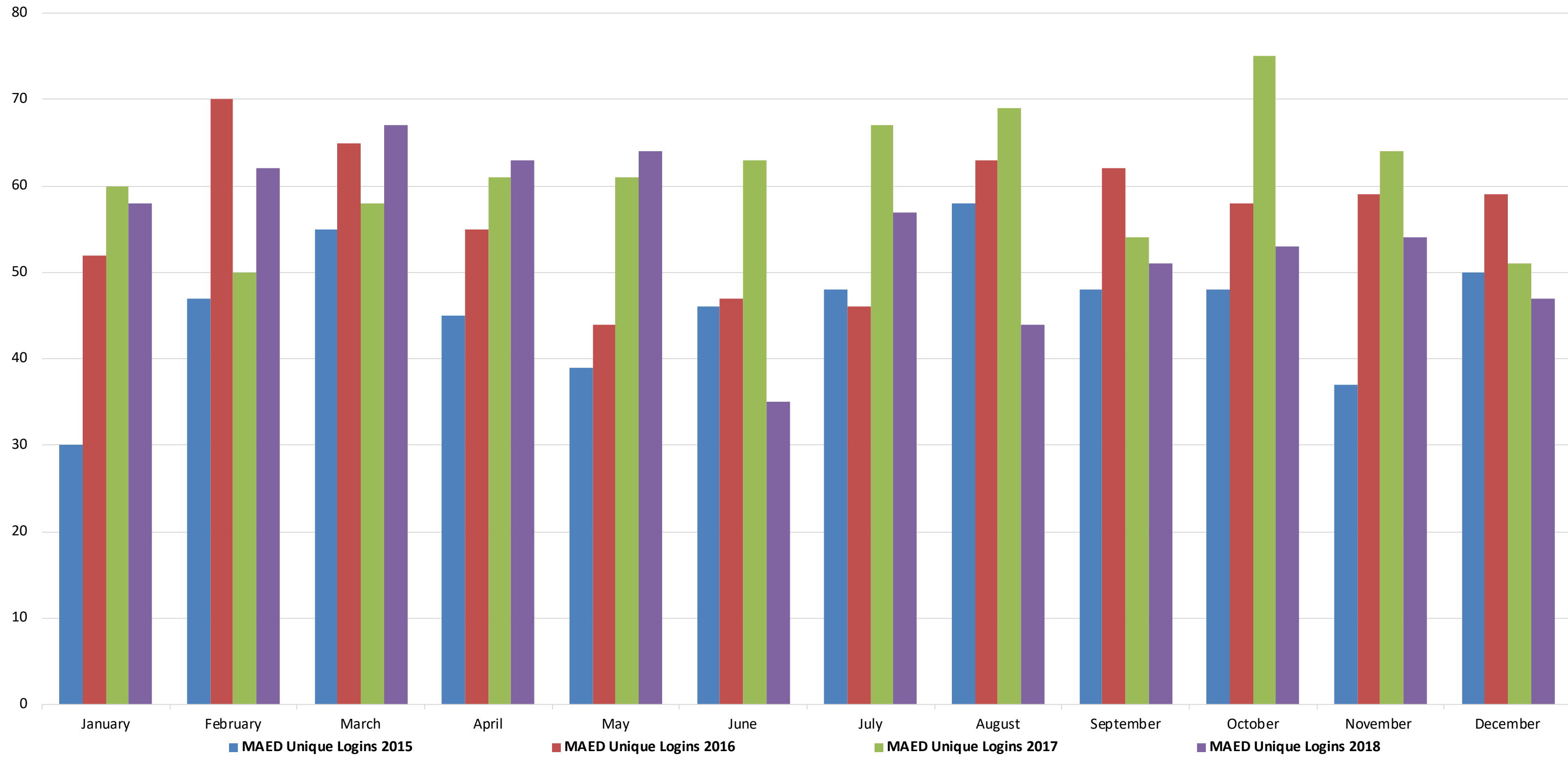
* after SMQ name indicates SMQ with narrow terms only. Broad search will yield the same results.
Number in parenthesis before SMQ name represents SMQ level.
P-values should be used for ranking purposes only, not for determining statistical significance.
Adverse Event terms, Relative Risk (RR) and Odds Ratio (OR) will appear in bold text if Continuity Correction was applied.

SMQ (Narrow Search)				Group Treatment (N = 525)			Placebo (N = 268)			Group Treatment vs. Placebo								
Level 1	Level 2	Level 3	Level 4	Event	Number subject	Propon (%)	Event	Number subject	Propon (%)	RD (per hund)	RD L (lower bo)	Upper bound	RR	RR L (lower bo)	Upper bound	OR	OR L (lower bo)	Upper bound
(1) Rhabdomyolysis/myopathy				0	0	0	1	1	0.37	-0.37	-1.1	0.36	0.17	0.007	4.17	0.17	0.007	4.179
(1) Acute renal failure				1	1	0.19	2	2	0.75	-0.56	-1.65	0.54	0.255	0.023	2.802	0.254	0.004	4.905
(1) Cardiac failure				1	1	0.19	0	0	0	0.19	-0.18	0.56	1.534	0.063	37.534	1.536	0.062	37.826
(1) Hepatic disorders				14	12	2.29	10	8	2.99	-0.7	-3.1	1.71	0.766	0.317	1.851	0.76	0.282	2.173
(1) Hepatic disorders	(2) Drug related hepatic disorders – comprehensive search			14	12	2.29	10	8	2.99	-0.7	-3.1	1.71	0.766	0.317	1.851	0.76	0.282	2.173
(1) Hepatic disorders	(2) Drug related hepatic disorders – comprehensive search	(3) Drug related hepatic disorders – severe events only		4	4	0.76	2	2	0.75	0.02	-1.26	1.29	1.021	0.188	5.539	1.021	0.145	11.356
(1) Hepatic disorders	(2) Drug related hepatic disorders – comprehensive search	(3) Drug related hepatic disorders – severe events only	(4) Hepatitis, non-infectious	1	1	0.19	0	0	0	0.19	-0.18	0.56	1.534	0.063	37.534	1.536	0.062	37.826
(1) Hepatic disorders	(2) Drug related hepatic disorders – comprehensive search	(3) Drug related hepatic disorders – severe events only	(4) Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions	3	3	0.57	2	2	0.75	-0.17	-1.39	1.04	0.766	0.129	4.555	0.764	0.087	9.207
(1) Hepatic disorders	(2) Drug related hepatic disorders – comprehensive search	(3) Liver related investigations, signs and symptoms		10	8	1.52	8	6	2.24	-0.71	-2.77	1.34	0.681	0.239	1.942	0.676	0.203	2.39
(1) Hepatic disorders	(2) Drug related hepatic disorders – comprehensive search	(3) Cholestasis and jaundice of hepatic origin		0	0	0	1	1	0.37	-0.37	-1.1	0.36	0.17	0.007	4.17	0.17	0.007	4.179
(1) Anaphylactic reaction				0	0	0	1	1	0.37	-0.37	-1.1	0.36	0.17	0.007	4.17	0.17	0.007	4.179

Introduction Groups SOC HLGT HLT PT Broad Algorithmic Narrow

The above report can be easily obtained following MAED launch through a web browser. The input data for these analyses are end-user supplied and can be clinical trial datasets or post-marketing datasets. Items in the red box indicate SMQs options

Figure 1: MAED Unique Login Growth



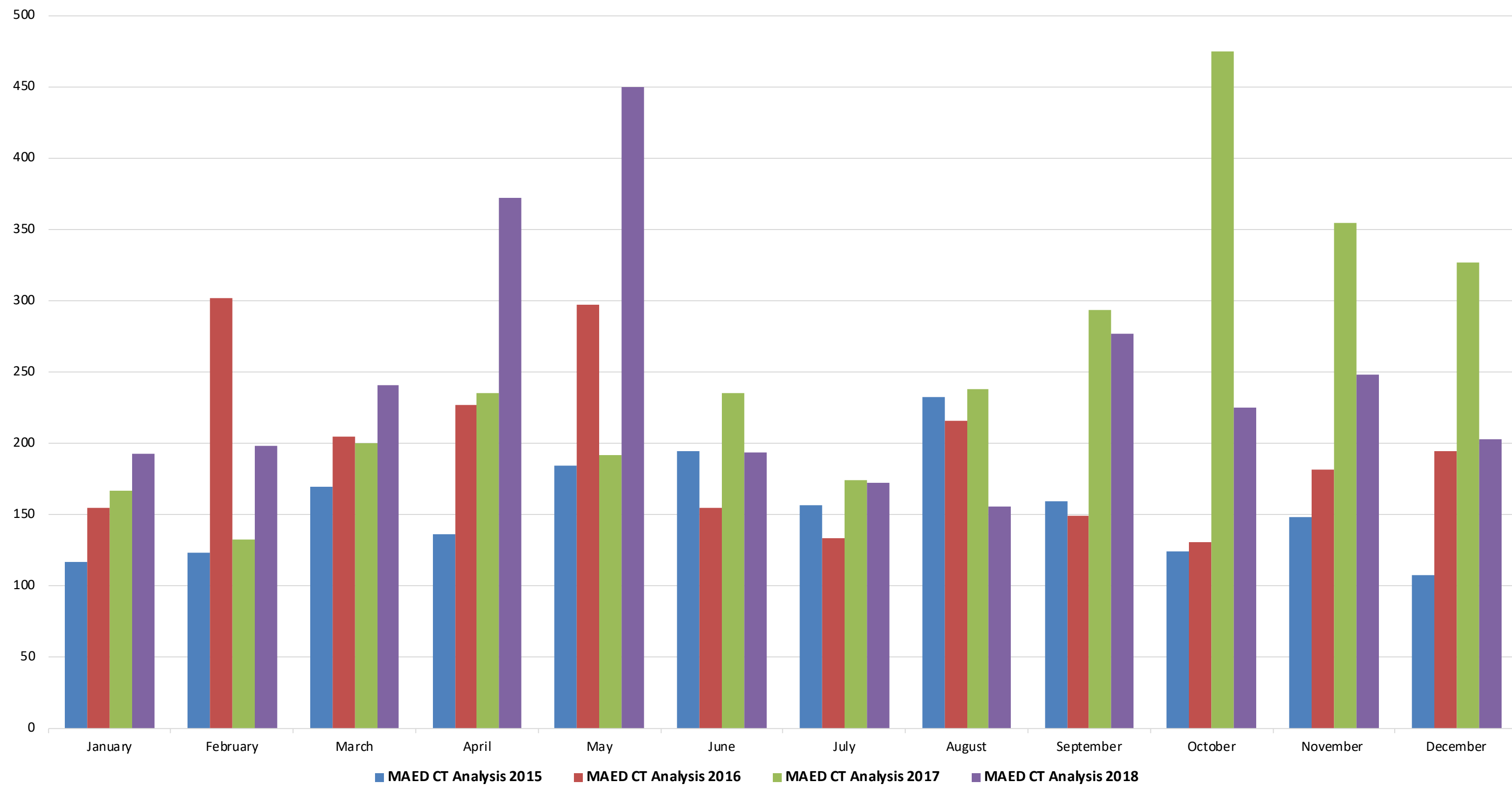
Methodology and Maintenance

The successful deployment, maintenance and upgrading of MAED Tool is due to a number of factors; it is the single tool that is served by a server environment maintained by the OCS, the architecture design is clear and scalable, project management is run using Agile methodology and uses JIRA as tracking system; regular releases include bug fixes and security updates

Given updates of the MEdDRA dictionary, source code maintenance is managed and reviewed in SonarCube as a standard process. MAED Tool updates MedDRA dictionary twice a year and also updates analysis algorithm for the algorithmic SMQ accordingly. The use of Puppet Automated Deployment Tool reduces risk and speeds deployment. EPLC and Application configuration are well maintained and documented. Since 2015 when metrics were first collected, the number of users (Figure 1) and frequency of analyses (Figure 2) per user have increased. CBER users have also started using MAED.

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily represent the policy of FDA.

Figure 2: MAED Analysis Growth



What's next?

MAED is a powerful signal detection tool widely adopted by reviewers in the Office of New Drugs, Office of Surveillance and Epidemiology, and the Office of biostatistics at CDER. To enable increased functionality, OCS is looking into further improvements to the end-user experience. There include incorporation of FDA internal review-based Customized MedDRA Query, broadening use in postmarketing use by pilot testing using FAERS data and analytic approaches used for postmarket reports. To enable this scale up of use, OCS needs to add support to existing OIMT governance, more Agile-friendly and explore opportunities to further improve the tool. The successful deployment and maintenance of MAED over 10 years serves as a model for enterprise tool development and maintenance.

