Impact of FDA's regulatory actions on the quality of REMS survey methodology protocols (2007 – 2020)

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Background

- Since 2007, FDA has had the authority to require risk evaluation and mitigation strategies (REMS) to ensure the benefits of a drug outweigh its risks.[1]
- REMS are risk management plans that use various strategies such as a Medication Guide (MG), communication plan (CP), elements to assure safe use (ETASU) (e.g., prescriber and dispenser training and certification, patient monitoring and enrollment), and certain packaging and disposal technologies.[2]
- Most REMS strategies that have a goal related to knowledge, employ surveys to evaluate patients' or healthcare providers' understanding of the serious risks associated with, and safe use of these drugs.
- On June 7th, 2012, the Agency held a public workshop to initiate dialogue among regulators and other stakeholders about survey methodologies that can be used to assess REMS knowledge goals, entitled "REMS Assessments: Social Science Methodologies to Assess Goals Related to Knowledge."[3]
- On February 1st, 2019, FDA released a draft guidance to describe best practices for the design, conduct and data analysis of the results of REMS knowledge surveys, titled "Survey Methodologies to Assess REMS Goals that Relate to Knowledge."[4]

Objectives

To evaluate the effect of the 2012 REMS workshop and 2019 draft guidance on the quality of REMS survey methodology protocols submitted to the agency.

Content Analysis Tool

To enable easy comparison of the protocols, a content analysis tool was created based on the "core scientific elements" (here forth referred to as core elements) described in the 2019 draft guidance and grouped into six domains.

Study method

Study design: Content analysis of survey protocols submitted to the agency segmented by the following regulatory time periods.

Pre workshop
09/27/2007 – 10/30/2012

Post workshop
11/01/2012 – 02/28/2019

Post draft guidance
03/01/2019 – 12/31/2020

Criteria: Index (FDA naïve) protocols of all CDER approved single product REMS with ETASU with a knowledge survey, that were available electronically.

Data collection: Each protocol was scored against the 52 core elements. Two reviewers independently adjudicated 10% randomly selected protocols among the three time periods (Average IRR: 91%).

Analysis: Descriptive analysis and statistical comparison of the mean scores using ANOVA whilst adjusting for multiple comparisons (Tukey's HSD).

Results

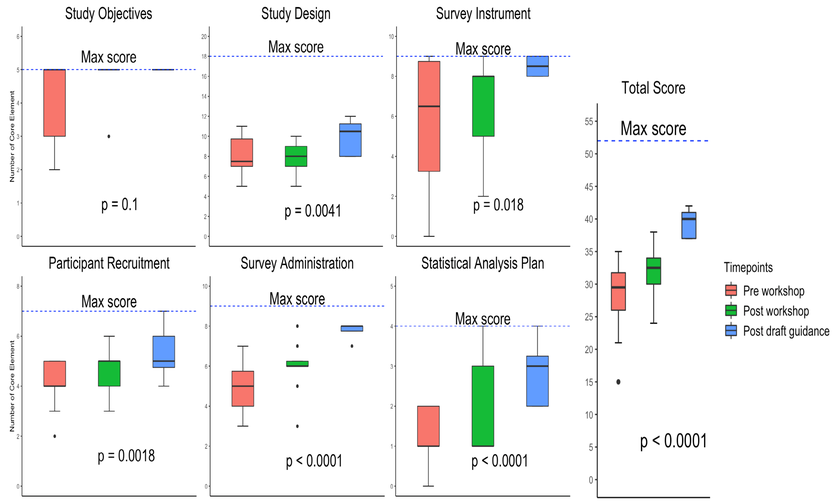
Key finding: The scientific rigor of survey protocols submitted to FDA improved over time. Evidence suggests the public workshop and draft guidance were associated with a positive impact, but scientific quality gaps remain

Table 1: REMS survey protocol characteristics

	Number of Survey protocols (N = 78) n (%)
Type of Application	
NDA	57 (73.08%)
BLA	21 (26.92%)
Time periods	
09/27/2007 - 10/30/2012	30 (38.46%)
11/01/2012 - 02/28/2019	40 (51.28%)
03/01/2019 - 12/31/2020	8 (10.26%)
Vendor involvement	61 (78.21%)
¶Type of REMS	
Medication guide (MG)	40 (51.28%)
Communication plan (CP)	32 (41.03%)
ETASU	
Prescriber certification	76 (97.44%)
Pharmacy certification	52 (66.67%)
Restricted settings	22 (28.21%)
Evidence of safe use	24 (30.77%)
Patient monitoring	16 (20.51%)
Registry	18 (23.08%)
Type of Stakeholder survey	
Prescriber	38 (48.72%)
Patient	30 (38.46%)
Pharmacist	6 (7.69%)
Non -prescribing HCP	2 (2.56%)
*Healthcare provider	1 (1.28%)
Healthcare facility	1 (1.28%)

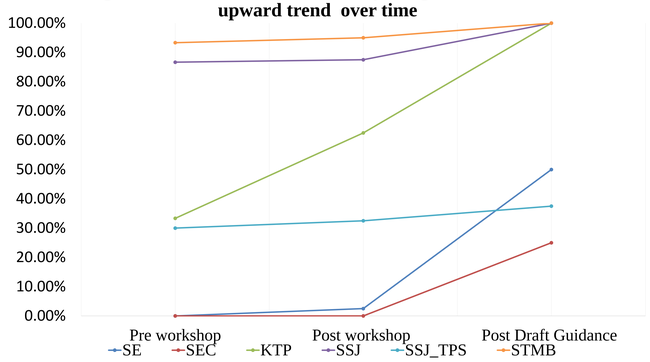
¶Type of REMS components is not mutually exclusive and does not add up to 100%
*Type of Healthcare provider was not specified

Figure 1: Statistical comparisons of mean scores for each domain and total score among the time periods



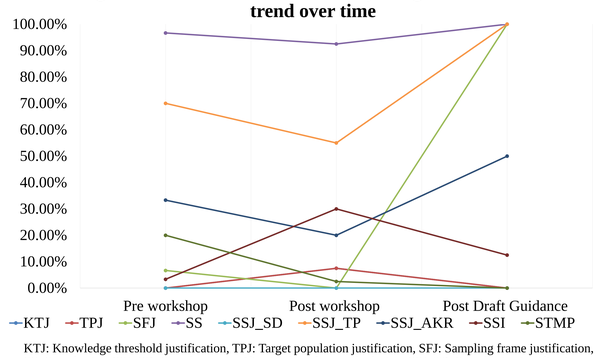
- Overall, mean scores **improved significantly** over time (p<0.0001), however, the maximum score a protocol received was a score of 42 out of 52.
- Among the domains study design, survey instrument, participant recruitment, survey administration and statistical analysis plan **improved significantly** over time (p=0.0041, p=0.018, p=0.0018, p<0.0001 and p<0.0001 respectively) whilst study objective improved but was **not statistically significant** (p = 0.1).

Figure 2. Core elements under study design that show an upward trend over time



SE: Study endpoint, SEC: Study endpoint calculation, KTP: Knowledge threshold percent, SSJ: Sample size justification, SSJ_TPS: Sample size justification based on target population size, STMB: Steps to minimize bias

Figure 3. Core elements under study design that show no trend over time



KTJ: Knowledge threshold justification, TPJ: Target population justification, SFJ: Sampling frame justification, SS: Sample size, SSJ_SD: Sample size justification based on study design, SSJ_TP: Sample size justification based on target population, SSJ_AKR: Sample size justification based on assumed knowledge rate, SSI: Sample size invite, STMP: Steps to maximize participation

- In general, core elements showed an upward trend among the time periods (Figure 2), however, there were other core elements that did not show any trend (Figure 3).
- This effect was consistent with the core elements in the other domains including study objectives, survey instrument, participant recruitment, survey administration, and statistical analysis plan.

Discussions

- The quality metrics of survey methodology protocols improved over time based on the presence of the core elements in this study, suggesting a positive effect of the two regulatory activities.
- There was an upward trend of the presence of core elements after the REMS workshop, which underscores the impact of FDA public workshops on the submissions of regulatory applications to the agency for review and approval.
- Characteristically, core elements domains for the time period after the release of the draft guidance received the most scores, and in certain situations, received the maximal score, suggesting a greater impact of the draft guidance on the quality of survey methodology protocols submitted to the agency.
- Despite the improvement observed, the maximum score a protocol received was less than the maximum allowable score, suggesting that survey methodology protocols submitted to the agency still lack the content of core elements.
- Moreover, majority of the core elements that did not show any trend over time include the various justification provided for the selection of the sampling frame, target population, knowledge threshold, etc.,. This could be as a result of these core elements having similar meaning or may not be clearly defined and as such might require consideration in finalizing the draft guidance.

Limitations

- This study evaluated the inclusion of the core elements and did not assess the quality or accuracy of the information presented in the protocols.
- This study did not assess the survey instrument itself, hence, the change over time observed cannot be said of the instrument itself, nor of its corresponding knowledge evaluation.
- The time period after the release of the draft guidance is relative shorter and includes a smaller number of protocols therefore, the full impact of the guidance may be underrepresented.
- This study was based on the draft guidance and there may be changes to the core elements as the guidance is finalized.

Conclusion

- Survey methodology protocols improved over time reflecting the effects of the regulatory actions.
- Despite the improvement, there still exist discrepancies or quality gaps in the quality of submitted REMS Survey methodology protocols based on the inclusion of core elements.

References

1. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. IX, 121 Stat. 823 (September 27, 2007).
2. U.S. Food and Drug Administration. Format and Content of a REMS Document. Draft Guidance for Industry. October 2017.
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4. U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. Issue Paper. June 7, 2012.