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CDER's Clinical Investigator Site Selection Tool

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ABSTRACT

CDER's Clinical Investigator Site Selection Tool (CISST) is a model developed to identify quantitative and qualitative risk attributes at the application, study, and site-level. The model relies on both Agency data feeds and on clinical investigator site summary data that is provided by applicants. Via standardized data exploration methodology, it provides a risk ranking of clinical investigator sites that serves as a framework for reviewers to select sites for bioresearch monitoring inspections. We will discuss the impact of CISST use on time to site identification for inspection, and identification of sites with good clinical practice non-compliance issues. Additionally, we will discuss how accumulating CISST data has been used to explore the global distribution of clinical investigator sites and enrollment of trial participants in pivotal trials submitted to CDER.

INTRODUCTION

Because the reliability of clinical trial data is critical to the approval decision, all Center for Drug Evaluation and Research (CDER) review disciplines share responsibility for evaluating data integrity. CDER's Office of Scientific Investigations (OSI), in the Office of Compliance, has specific responsibility for verifying the integrity of data submitted to CDER in support of applications and supplements, and for determining whether clinical trials are conducted in compliance with applicable FDA regulations and statutory requirements, including those intended to ensure the rights and welfare of human research subjects.

To meet its review performance goals in accordance with CDER good review management principles and practices for products covered by the Prescription Drug User Fee Act (PDUFA), CDER generally initiates inspection planning for premarketing inspections to evaluate clinical investigator compliance with good clinical practice principles early in the application review process (i.e., during the filing determination and review planning phase). CDER's inspection planning includes (1) the selection of clinical investigator sites and other regulated entities for on-site inspections, and (2) the preparation of assignment memos and background packages that are provided to Office of Regulatory Affairs (ORA) investigators that perform on-site inspections under FDA's bioresearch monitoring (BIMO) program. To facilitate discussions on whether clinical investigator inspections are needed, and when needed, selection of clinical investigator sites for inspection, CDER has developed a risk-based model. Staff in CDER's Office of New Drugs (OND), Office of Biostatistics (OB), Office of Computational Science (OCS), and Office of Scientific Investigations (OSI) contributed to the development of CISST and remain engaged in its further development and routine use for site selection.

The model uses a summary level clinical site dataset ("clinsite"[1] that is provided by applicants in their NDA and BLA submissions). In addition, it uses CDER data sources that contain information related to clinical investigators' history of participation in regulated research, inspectional history, and any referrals, complaints or incident reports that may have been received regarding clinical investigators. These data are used in the CISST to describe and summarize the characteristics and outcomes of clinical investigations, both at the study level and at the level of the individual study site. The model provides reviewers a risk ranking of sites in a standard framework and promotes standard methods for data exploration to be used for clinical investigator site selection. It gives reviewers the ability to choose clinical investigator sites for inspection based on review of data irregularities, outlier analyses with filters, comparison of variables across treatment arms, clinical investigator participation across multiple studies, clinical investigator experience and inspectional history, and review of regional and country specific summaries. The CISST also provides for automated documentation of reason(s) sites are selected (or not selected) for inspection and contains

[1] For a description of the format and content of the "clinsite" dataset, see FDA draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions Guidance for Industry* available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf, and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

automated form generation capabilities. CISST data, and "clinsite" receipt and usage data, are also archived in central databases to permit further evaluation of these data across applications.

DATA SOURCES

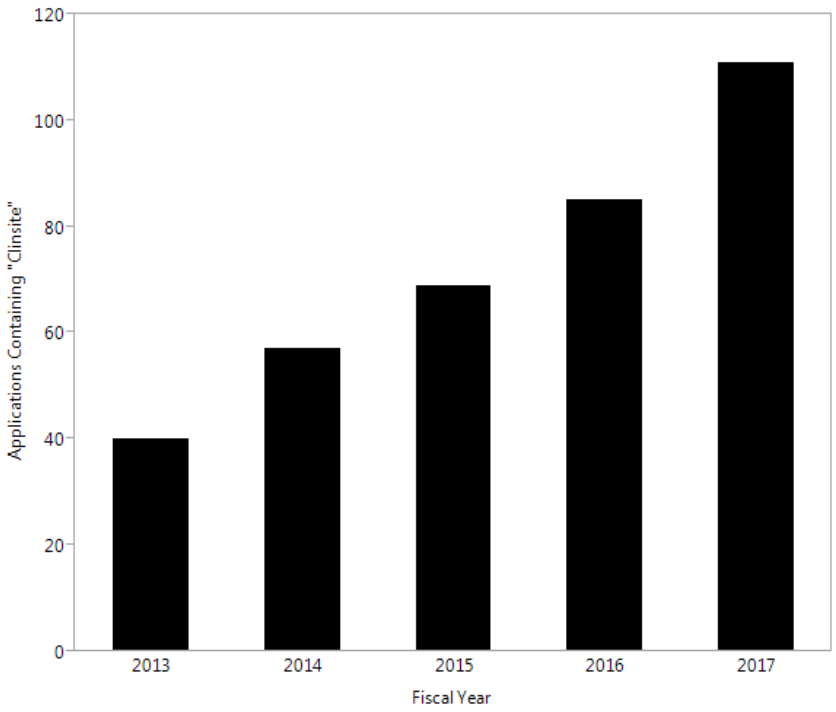
Data sources for analyses presented in this paper include: 1) CISST database, 2) Compliance Program Information System (COMPLIS), and 3) Document Archiving Reporting and Regulatory Tracking System (DARRTS). Data for NDAs and BLAs (original and supplements containing clinical data) submitted to CDER for fiscal years 2013 through 2017 were used to generate analyses of CISST submission and use, time to identification of clinical investigator sites for inspection, and inspectional outcomes. For the analyses of global clinical investigator site and subject enrollment distribution, data in the CISST database for FY2010 through FY2015 was utilized.

FINDINGS

SUBMISSION AND USE OF SUMMARY SITE LEVEL DATASET BY FISCAL YEAR

The number of "clinsite" datasets submitted by Applicants in original NDAs and BLAs, and in NDA and BLA supplements has increased steadily between FY2013 and FY2017. Figure 1. summarizes the number NDA and BLA submissions for which "clinsite" submissions were received, processed into CISST, and distributed to reviewers. In some cases, a single "clinsite" dataset may contain data supporting more than one original application or supplement. For example, when both oral and intravenous versions of a drug product were studied within the same studies a single "clinsite" dataset may have been provided in support of both the NDA for the oral formulation and the NDA for the intravenous formulation.

FIGURE 1. APPLICATIONS CONTAINING "CLINSITE" DATASET BY FISCAL YEAR



Submitted "clinsite" datasets are identified daily by search of eCTD submissions received over the prior 24 hours for key words ("BIMO", "clinsite"). If correctly formatted as requested, "clinsite" data along with Agency data are loaded to the CISST and the loaded CISST undergoes a quality control process to ensure data in the CISST accurately reflects data and data summaries provided elsewhere in the submission. The loaded CISST is then distributed to OND, OB, and OSI reviewers to be used to assist in determine whether clinical investigator inspections are needed, and when inspections are considered needed, selection of clinical investigator sites for inspection. For submissions containing "clinsite" at initial submission, and acceptably formatted (required no more than minor formatting revisions that could be readily resolved by CDER staff), in fiscal year 2017 the median time to prepare and distribute loaded CISSTs to reviewers for use was 5 days. Data for "clinsite" datasets received in advance of the initial NDA or BLA submission (for example, as a submission to the IND or as part of a rolling review) are not included in this summary statistic.

TIME TO IDENTIFICATION OF CLINICAL INVESTIGATOR SITES FOR INSPECTION

One of CDER's goals in development of the CISST was to enable review staff to meet good review management practices, as described in the 21st Century Review Process Desk Reference Guide, which specifies that a decision about the need for routine BIMO inspections and identification of sites for which BIMO inspections will be performed should be determined by submission day 30 for applications on a priority review clock and by day 45 for applications on a standard review clock. To evaluate the impact of CISST use on time to selection of clinical investigator sites for inspection, the time from date of submission to date of confirmation of clinical investigator sites selected (date of consult request in DARRTS) was calculated for all NDA and BLA submissions for which clinical investigator site inspections were requested. Table 1. provides a summary of mean and median days expended to identify sites for inspection based on CISST use. Use of the CISST has resulted in a mean reduction in time to identification of clinical investigator sites for inspection of 10 days and 18 days for applications on priority and review clocks, respectively.

TABLE 1. OVERALL FY2013 TO FY2017 SUBMISSIONS - TIME TO DETERMINATION CLINICAL INVESTIGATOR SITES FOR WHICH BIMO INSPECTIONS WILL BE CONDUCTED

DAYS TO REVIEWER DETERMINATION OF CI* SITES FOR INSPECTION	PRIORITY REVIEW		STANDARD REVIEW	
	CISST** NOT USED	CISST** USED	CISST** NOT USED	CISST** USED
	(N***= 153)	(N***= 122)	(N***= 204)	(N***= 129)
MEAN DAYS	39	29	71	53
MEDIAN DAYS	36	31	67	51

*CI = CLINICAL INVESTIGATOR, **CISST = CDER'S CLINICAL INVESTIGATOR SITE SELECTION TOOL, ***N = NUMBER OF APPLICATIONS FOR WHICH CI INSPECTIONS CONDUCTED

INSPECTION OUTCOMES

Based on available resources, in general, FDA can inspect less than one percent of all clinical investigator sites contributing data to studies in NDA and BLA submissions. Therefore, another of CDER's goals in development of the CISST was to assist reviewers in identification of clinical investigator sites that may be at increased risk of non-compliance with good clinical practice principles and thereby represent the most risk to the protection of trial participants' rights, safety, and welfare, and to the data integrity of the study. To evaluate the impact of CISST use on inspection outcomes, the final classification of clinical investigator site inspections for was calculated for all NDA and BLA submissions for which clinical investigator site inspections were requested for fiscal year 2012 through fiscal year 2016 submissions. Because final classifications for many inspections related to fiscal year 2017 submissions were pending at the time of this analysis, fiscal year 2017 data are not included. Table 2. provides a summary of final inspection classification based on CISST use. For the time-period examined, reviewer use of the CISST to identify clinical investigator sites for inspection has resulted in a 7.16% increase in identification of sites with regulatory violations and final classifications of Voluntary Action Indicated or Official Action Indicated when compared to reviewer site selections using alternate methods.

TABLE 2. FINAL INSPECTION CLASSIFICATION FY2013 TO FY2016 SUBMISSIONS BASED ON USE OF CISST TO SELECT CLINICAL INVESTIGATOR SITES FOR WHICH BIMO INSPECTIONS WILL BE CONDUCTED

INSPECTION FINAL CLASSIFICATION	CISST* NOT USED N** = 800 (%)	CISST* USED N** = 585 (%)
NO ACTION INDICATED	566 (70.75%)	371 (63.42%)
VOLUNTARY ACTION INDICATED	227 (28.38%)	206 (35.21%)
OFFICIAL ACTION INDICATED	7 (0.86%)	8 (1.37%)

*CISST = CDER'S CLINICAL INVESTIGATOR SITE SELECTION TOOL, **N = NUMBER OF CLINICAL INVESTIGATOR INSPECTIONS FOR WHICH INSPECTION FINAL CLASSIFICATION AVAILABLE

GLOBAL DISTRIBUTION OF CLINICAL INVESTIGATOR SITES AND SUBJECT ENROLLMENT

Accumulating data in the CISST database for "clinsite" submissions FY2009 through FY2016 was used to explore the global distribution of clinical investigator sites and enrollment of trial participants in pivotal trials submitted to

CDER in support of marketing applications. Clinical investigator site locations were identified using submitted address data for each site listed in archived "clinsite" datasets. For the time-period examined, the CISST database contains data for 729 clinical studies (primarily pivotal phase 2 and phase 3 studies submitted in support of efficacy and safety claims), 69,370 clinical investigator sites, and 902,203 enrolled subjects. As not all applicants elected to submit the "clinsite" dataset, these data represent a subset of all data submitted to CDER in support of marketing applications. Table 3. provides a summary of clinical investigator sites and subject enrollment by country for CDER applications containing the "clinsite" dataset.

TABLE 3. GLOBAL DISTRIBUTION OF CLINICAL INVESTIGATOR SITES AND SUBJECT ENROLLMENT IN "CLINSITE" SUBMISSIONS FY2009 THROUGH FY2016

COUNTRY	NUMBER CLINICAL INVESTIGATOR SITES	NUMBER SUBJECTS ENROLLED	COUNTRY	NUMBER CLINICAL INVESTIGATOR SITES	NUMBER SUBJECTS ENROLLED
Algeria	10	158	Lithuania	218	2291
Argentina	1363	17894	Malaysia	241	2593
Australia	1095	11048	Mexico	959	14603
Austria	350	3942	Moldova, Republic of	9	78
Belarus	33	394	Morocco	5	64
Belgium	737	6825	Netherlands	751	12417
Belize	3	181	New Zealand	200	2151
Bosnia and Herzegovina	19	155	Norway	267	3482
Brazil	1017	19416	Panama	16	97
Bulgaria	624	9916	Peru	415	4108
Canada	2601	33199	Philippines	305	3677
Chile	377	4416	Poland	1861	32261
China	710	10539	Portugal	289	2153
Colombia	354	8097	Puerto Rico	142	927
Costa Rica	2	28	Qatar	1	2
Croatia	153	1505	Romania	1047	12740
Czech Republic	1057	16038	Russian Federation	2423	31642
Denmark	655	9100	Rwanda	1	80
Dominican Republic	15	486	Saudi Arabia	9	91
Egypt	26	387	Serbia	138	1560
Estonia	185	1891	Sierra Leone	5	14
Finland	353	6524	Singapore	75	742
France	1659	14671	Slovakia	480	5557
Georgia	127	3640	Slovenia	38	238
Germany	2747	30099	South Africa	805	10105
Greece	279	2573	Spain	1657	14730
Guatemala	111	1313	Sri Lanka	6	125
Honduras	3	90	Sweden	565	6438
Hong Kong	83	1988	Switzerland	197	1668
Hungary	1172	16703	Taiwan	530	4842
India	1237	17092	Tanzania	1	396
Iran, Islamic Republic of	8	21	Thailand	212	2453
Ireland	69	354	Tunisia	19	246
Israel	791	9116	Turkey	416	3200
Italy	1487	13296	Ukraine	1115	15576
Japan	2044	14905	United Arab Emirates	3	45
Kenya	4	273	United Kingdom	1703	16191
Korea, Republic of	1063	9912	United States	27370	391646
Latvia	226	2622	Vietnam	5	15
Lebanon	22	152			

CONCLUSION

The submission of "clinsite" datasets has risen steadily and is anticipated to continue to increase in coming years. The recently released *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* (February 2018) contains revised formatting and data specifications that should further assist sponsors in

development of the requested “clinsite” dataset. In addition, the development of data standards to address site summary level data needs is underway, and once available, will further assist sponsors.

Accumulating data on CISST usage demonstrates improved time to identification of clinical investigator sites for which BIMO inspections will be conducted when the CISST is available to reviewers, which is advantageous because it aids good review management practices, as described in the 21st Century Review Process Desk Reference Guide. In addition, the earlier identification of sites for inspection facilitates the completion of inspections earlier in the review cycle, which may provide applicants the opportunity to address significant inspection observations earlier in the review process.

Data trends suggest that use of the CISST to select clinical investigator sites for inspections, as opposed to other methods used for site selection by CDER reviewers, results in increased identification of sites with regulatory violations (final inspection classifications of Voluntary Action Indicated and Official Action Indicated). Further exploration of inspection outcome data is needed to determine whether specific variables used in the CISST are more predictive of inspection outcomes and whether adjustment to risk weighting of variables in the CISST may be indicated.

Examination of archived “clinsite” data in the CISST database presents unique opportunities to look at data across CDER NDA and BLA submissions by location of clinical investigator sites because the “clinsite” datasets include investigator addresses. The global distribution of clinical investigator sites and subject enrollment presented in this paper provides an example of analyses that may be conducted. Additional datamining efforts, for example looking at patterns of safety data reporting by geographic location, are also being explored.

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