NOVEL INSIGHTS IMPROVE DATA QUALITY & INCREASE PATIENT SAFETY

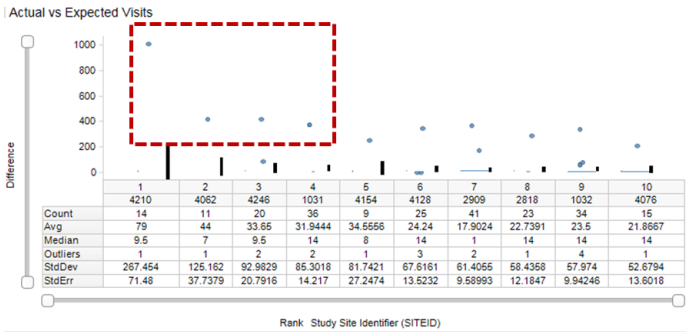
Central monitoring integrates data across sites, analyzes trends and enables novel insights that would be otherwise unavailable to individual on-site monitors.

IDENTIFICATION OF REGIONAL AE UNDER-REPORTING PATTERN

On an injectable IP study, early signals indicated underreporting of AEs when comparing US and EMEA. US sites had significantly lower AE reporting rate then EMEA when reporting AEs of Injection Site Reactions (ISR). Because of an early detection trend, 78 ISRs were added for events that occurred prior to the escalation, and total of 323 new ISR events were added in 3-month period following the escalation.

The **data shared with the clinical team would not be obvious during a single site on-site visit**, and therefore the drug safety profile might have looked significantly different if RBM had not enabled early insight into this risk and the ability to address it in the first months of enrollment and dosing. **RBM enabled earlier insights and increased patient safety**.

IDENTIFYING PROTOCOL DEVIATIONS VIA VISIT WINDOW



	1	2	3	4	5	6	7	8	9	10
	4210	4062	4248	1031	4154	4128	2909	2818	1032	4076
Count	14	11	20	36	9	25	41	23	34	15
Avg	79	44	33.65	31.9444	34.5556	24.24	17.9024	22.7391	23.5	21.8667
Median	9.5	7	9.5	14	8	14	1	14	14	14
Outliers	1	1	2	2	1	3	2	1	4	1
StdDev	267.454	125.162	92.9829	85.3018	81.7421	67.6161	61.4055	58.4368	57.974	52.6794
StdErr	71.48	37.7379	20.7916	14.217	27.2474	13.5232	9.58993	12.1847	9.94246	13.6018

RBM revealed sites and subjects showing potential protocol non-compliance via visit window delays, as captured by data trend analysis. This resulted in **identifying protocol deviations early** in the study life-cycle to help outlier sites get trained and monitored to prevent recurrence.

HARMONIZING DEFINITIONS & REDUCING INCONSISTENCIES

ACRO members have observed negative impacts of inspection inconsistencies, both within the FDA, and between the FDA and EMA/other Regulators.

WHAT DO QTLS MEAN UNDER R2? IT DEPENDS ON WHO YOU ASK

Quality Tolerance Limits (QTLs) were introduced in ICH E6 (R2). Some inspectors have interpreted QTLs as a threshold that, if breached, means the study is no longer compliant with GCP. Others interpret QTLs as a signal – the point at which investigation (and potentially action) is needed to prevent challenges in the ability to use the study data and/or prevent harm to subjects. The latter is the view linked to QbD principles: identify what's critical to quality for a study, streamline and tailor trial design to prevent risks in those critical areas if feasible, and establish mechanisms to swiftly detect and respond if a risk starts to materialize (e.g. when a QTL is reached). ACRO sees value in **utilizing the QTLs as an early warning signal to take action**, not the point at which to decide a study has so many ineligible subjects that statistical significance is lost.

INSPECTION CONTEXT HASN'T SHIFTED TO ACCOUNT FOR R2

The agency has an opportunity to ensure that monitoring plans are shared with FDA field investigators as part of their background package and that FDA field investigators are well-versed in not only relevant guidance but the science/ design of clinical trials to be able to evaluate what are and aren't "errors that matter."

ACRO

STRENGTHENING RBM GUIDANCE WILL FACILITATE INDUSTRY ADOPTION

Key points from ACRO's comment letter:

A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers
(Docket # FDA-2019-D-0362 | March 2019)

- **A stronger statement about the place of risk-based monitoring** in the oversight toolbox would be useful. We suggest the following:

  > While traditional approaches to monitoring, including on-site monitoring and 100% SDV /SDR, will be appropriate under specific circumstances, FDA believes risk-based monitoring represents a ***best practice*** [emphasis added] to allow sponsors to identify and address issues during the conduct of clinical investigations.

- The Q&A guidance does not **resolve questions within the industry about the definition of central monitoring**. Specifically, does centralized monitoring include traditional data cleaning activities, like listings reviews, programmed complex edits, frequencies, etc., in addition to newer, technology enabled activities, such as statistical analyses, key risk indicators and outlier identification? Additional clarity in this definition would be welcomed by industry.
- In advising sponsors about how they should focus oversight activities, we suggest the following:

  > Sponsors should determine the types and intensity of monitoring activities best suited to address the identified risks, most often beginning with centralized monitoring, and then progressing to other monitoring activities as indicated. Further, **we suggest routine use of statistical and analytical methods to monitor all critical data in a centralized way and thereby drive adjustment of monitoring activities and the focus of trial oversight**.

- In the Q&A discussion of the risk-based approach to monitoring, ACRO appreciates the straightforward description of some of the **advantages of centralized monitoring capabilities**. Certainly, early identification of trends relating to missing data and/or protocol deviations/violations allows for root cause analysis and timely corrective actions. In fact, it might be useful to insert the following statement:

  > FDA encourages the use of centralized monitoring practices. Centralized monitoring offers benefit in terms of faster review of newly entered patient visits and focuses on aggregate data review and analysis.

- In the discussion of the elements of monitoring plans, we suggest **a clearer commitment to SDR sampling**, as per this note from the 2013 guidance:

  > For example, for a particular study, there may be minimal benefit in comparing 100% of the source data for each subject to the CRFs for each study visit. Rather, it may be sufficient to compare the most critical data points for a sample of subjects and study visits as an indicator of data accuracy. Similarly, for a particular study, although collection of all concomitant medications, body temperature, and body weight are required by the protocol and are documented in the medical record and transcribed to a CRF, they may not be identified by the sponsor as critical data, because a small error rate in those variables would not affect the outcome of the trial.

- To **add clarity in the content of monitoring plans**, ACRO recommends that, as long as one of the plans includes the components outlined (or most of them), then the other functional plans which cover "central monitoring" will not need all of the components listed. In addition, it would be useful for the agency to clarify that "central monitoring" includes traditional data cleaning activities.

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