

SUBMITTED ELECTRONICALLY

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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1062
Rockville, MD 20852

**RE: A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers
Guidance for Industry**

Docket Number: FDA-2019-D-0362

Dear Colleagues:

Introduction

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all FDA-regulated clinical investigations worldwide.

With more than 130,000 employees engaged in research activities in every U.S. state and 114 countries around the world, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

We thank the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA or the Agency) for issuing the above-referenced Q&A guidance, which expands on the guidance for industry, *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring*, (the RBM guidance) originally issued in 2013.

General Comments

On March 6, 2019, less than 10 days before the above-referenced guidance was published in the *Federal Register*, a group of ACRO member company representatives met with the Director of the Center for Drug Evaluation and Research and other senior CDER personnel for a discussion of risk-based monitoring. Before offering specific responses to the Questions and Answers Guidance, ACRO is pleased to review our perspective on the current state of RBM adoption and implementation.

ACRO provided to CDER a short document entitled **The Risk-Based Monitoring Landscape In 2019**, which is attached here. Based on surveys of ACRO member companies, we reported that adoption of RBM technologies is growing rapidly. To illustrate, in 2016, new trial starts using RBM technology comprised less than 20 percent of all new starts; by 2018, as reported by ACRO member companies, that proportion had risen to a majority of new trial starts. While different methodologies and interpretation of RBM exist, it is clear that at least some components of a RBM approach are being adopted widely.

We reported also that all ACRO member companies have made significant investments to advance RBM, via:

- New training and new positions to reshape the monitoring workforce to utilize new technologies and new processes;
- Building and partnering to deploy new technology and software solutions to support RBM product offerings; and
- Creating new processes integral to RBM to be deployed across sponsors, CROs, and investigative sites.

We reported, as well, quality, efficiency and speed metrics tracked in RBM-enabled trials by CROs and technology companies, with examples including:

- Enhanced ability to identify and manage patient eligibility, unreported adverse events, and protocol deviations;
- Reduction in data management cycle time, and faster time to database lock;
- Reduction in subject visit data entry lag;
- Cost savings, in some instances, on the order of 3-15 percent;
- And, in one matched-trials comparison a four-fold lower error rate in critical data in RBM trials compared to trials that utilized 100% SDV.

Notwithstanding these positive examples of improved monitoring results, and the very positive trend of RBM penetration, in the discussion with CDER ACRO company representatives reported that challenges limiting wider adoption of RBM methodologies remain.

These challenges include the perceptions that traditional oversight methods are “lower risk,” that the strategy of checking every data point is “safer,” and that 100% SDV is a way of ensuring data quality. These perceptions, which may be held by sponsors, CROs and sites alike, are reinforced then by regulatory inspections findings in which failures in non-critical data result in findings nonetheless. Further, varied interpretations of ICH E6 (R2) requirements by FDA and EMA inspectors create uncertainty for globally-distributed clinical trial projects and further “risk avoidance” and reliance on traditional oversight methods.

Unaware that a RBM Q&A guidance was soon to be released, the ACRO team suggested that the Agency could positively impact industry expectations and perceptions relating to RBM, in part by articulating in guidance more straightforward and stronger support for risk-based monitoring approaches as preferred methodologies for “oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the data submitted to FDA” [21 CFR part 312, subpart D and 21 CFR part 812, subpart C).

Specific Comments

Background Section

Unfortunately, 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, outlier identification? ACRO suggests

that many of these traditional activities to clean and validate data fall under the definition of central monitoring.

It appears to us that a number of functional plans would then also be expected to comply with the guidance:

1. In relation to the contents of the “monitoring plans” – which we interpret to mean either a single monitoring plan (onsite and central activities) or multiple plans (clinical monitoring plan, central monitoring plan, data management plan, statistical analysis plan, safety and medical management plan);
2. and in relation to the reports of central monitoring provided to a client on a regular basis.

In regard to the content of the monitoring plans, it is our recommendation 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, if the agency agrees that “central monitoring” includes these traditional data cleaning activities, then we would suggest clarifying that in Q6 and Q8.

ACRO believes that a stronger statement about the place of risk-based monitoring in the oversight toolbox would be useful. For instance, at line 47-48 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.”**

Further, we note that on-site monitoring is not synonymous with 100% or even 50% SDV/SDR, as there are many methods of on-site review of the conduct of the trial, subject safety and data integrity. Finally, we commend to the regulated industry the statement at ICH E6 (R2) 5.18.3 Addendum: “The sponsor should [emphasis added] develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).”

Q1. What is the purpose of the risk assessment and should sponsors document their methodologies and activities for assessing risk?

At line 63 we suggest a preliminary statement that, **“In designing a protocol that is safe, efficient and practicable, sponsors will assess potential risks to the rights and safety of subjects and to the collection of accurate and useful data. Then,** consistent with the RBM guidance, sponsors should identify and perform a risk assessment on those critical data and processes that are necessary for human subject protection and integrity of the investigation.”

Following the first sentence at lines 77-78, we suggest adding, **“The FDA understands that while the monitoring plan will address how identified risks are to be monitored, it will not cover all the functions included under the rubric of risk-based quality management. That is, we expect that a**

variety of functional management tools, such as a DSMB, will be utilized to protect subject safety and data quality, and not all of these will be pre-specified in the initial monitoring plan.”

Q2. Should sponsors monitor only risks that are important and likely to occur?

ACRO appreciates the process suggested at lines 84-90, describing RBM as first *focusing* oversight activities on important and likely risks, and then permitting monitoring activities to *evolve* as additional risks and issues are identified.

At lines 87-89, we suggest the following edit, “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 (type, intensity) and the focus of trial oversight.”**

Q3. What factors should sponsors consider when determining the timing, types, frequency, and extent of monitoring activities?

ACRO believes that the factors elucidated at lines 98 through 163 are reasonable and helpful. However, in order to more clearly indicate that the Agency is not suggesting that the factors to follow might be best addressed by traditional SDV/SDR monitoring, we suggest that the sentence beginning at line 95 be preceded by a statement indicating that: **“Informed by a risk assessment of the clinical trial, as they develop a risk-based monitoring approach,** factors sponsors should consider include the following:”

At lines 107-108 and 122-127 we applaud the inclusion of clinical investigation site variables in determining the timing, types, frequency, and extent of monitoring activities.

We suggest that line 112 be phrased as, **“data capture systems and related impact on data visibility for ongoing monitoring, e.g.,** electronic data capture to be utilized”

At line 120 we suggest: “FDA also recommends that sponsors consider the following additional factors, **which can be used to further adapt the method and frequency of monitoring based on site performance.”**

Also, because readers are highly sensitive to what they perceive as signals from the FDA, we believe that the examples given at lines 140-145 should be reversed, thus suggesting “early monitoring activities, for example, through remote processes,” before “scheduling an early monitoring visit”. A specific suggestion at line 142 would be, “(for example, through **centralized** processes)”

Q4. How can a risk-based approach to monitoring that includes centralized monitoring help minimize missing data, protocol violations, or protocol deviations?

ACRO appreciates this 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 an initial sentence at line 168: **“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.”

At the end of line 172 we suggest adding, **“Taking action in response to missing data or protocol deviations or violations discovered via centralized monitoring is a collaborative effort between the clinical investigator and CRO/sponsor. Therefore, the FDA recommends that corrective action strategies include consideration of site-level communication and education.”**

Q5. Should the risk-based monitoring approach include processes to ensure that appropriate blinding is maintained?

ACRO appreciates that ensuring the investigation blind can be critical to the scientific evaluation of product safety and efficacy. We do have some concern that calling out blinding with special emphasis in this Q&A guidance – as opposed to other key risks, such as consent, eligibility, primary endpoints, etc. – may engender a level of resistance from some investigators and sites that are reluctant to embrace centralized analysis and data visualization. Certainly, in reviewing laboratory findings, adverse events or efficacy data, it may be possible to see trends that may indicate which treatment arm a patient may be on. For this reason, we suggest that, at lines 178-179, the FDA emphasize more strongly that the responsibility of maintaining the investigation blind is held by the sponsor and not the investigator or site.

Q6. What elements should sponsors include in monitoring plans?

We believe that the elements listed at lines 202 through 246 are generally clear and helpful. Several specific comments follow here:

At lines 252-253: we note that the investigation design and the blinding and randomization procedures would be included in the study protocol, inclusion of which might be better listed at lines 208-210

At lines 255-257 we suggest re-wording as follows: **“Identify risk elements in the randomization process, to ensure that appropriate risk-mitigating actions are planned”**

At lines 259-261 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.”

At line 267 we suggest “approach for correcting these issues, **including root cause analysis”**

We would suggest two small edits at lines 270-271: “Sponsors are encouraged to develop **risk-based** monitoring plans that emphasize **processes to address** critical risks that have the greatest potential to adversely affect....”

Q7. How should sponsors follow up on significant issues identified through monitoring, including communication of such issues?

ACRO appreciates the list of examples of corrective and preventive actions at lines 288-290, and the recommendations regarding documentation and communication at lines 293-296.

ACRO believes that the expectation should be stated to document identified systemic issues to mitigations activities, including preventative actions, detectability and corrective actions, and their impact to the identified risks as identified within the risk register.

Q8. How should centralized monitoring activities and the results of these activities be documented and shared with those involved in the investigation?

At lines 304-311 it may be useful for the FDA to elaborate on its current thinking, rather than merely re-stating the 2013 guidance.

In addition we suggest that line 316 be extended as follows: “centralized monitoring activities that are relevant to the CI’s activities, **to the extent to which the CI’s activities relate to critical data and processes necessary for human subject protection and integrity of the investigation.**”

Conclusion

ACRO thanks HHS and the FDA for taking up an overdue updating of the RBM guidance.

ACRO looks forward to further dialogue with the Agency about current RBM adoption and ways that stakeholders, including sponsors, CROs, technology vendors, investigative sites, IRBs, DMCs, and other can spur implementation of methodologies that produce better quality data while protecting human subject rights, welfare and safety.

Respectfully submitted,



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Appendix A: Definitions

With the feedback provided, the following definitions¹ were referenced:

Monitoring is used in different ways in the clinical trial context. It can refer to the assessment of CI conduct, oversight, and reporting of findings of a clinical trial; to the ongoing evaluation of safety data and the emerging benefit-risk profile of an investigational product; and to the monitoring of internal sponsor and contract research organization (CRO) processes and systems integral to proposing, designing, performing, recording, supervising, reviewing, or reporting clinical investigations.

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted. Centralized monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

Source Data Review (SDR): Review of all records pertaining to the individual subject (e.g. medical records, lab results, Informed Consent Document (ICD), drug dispensing records, IVRS logs). Review of source documentation to check quality of source, review protocol compliance, ensure the critical processes and source documentation (e.g., accurate, legible, contemporaneous, original, attributable) are adequate, to ascertain CI involvement and appropriate delegation, and assess compliance to other areas (e.g., SOPs, ICH GCPs).

Source Document Verification (SDV): Commonly known as “transcription checking,” is the process by which data within the CRF or other data collection systems are compared to the original source of information (and vice versa) to confirm that the data were transcribed accurately (i.e., data from source matches data in the CRF or other systems and vice versa).

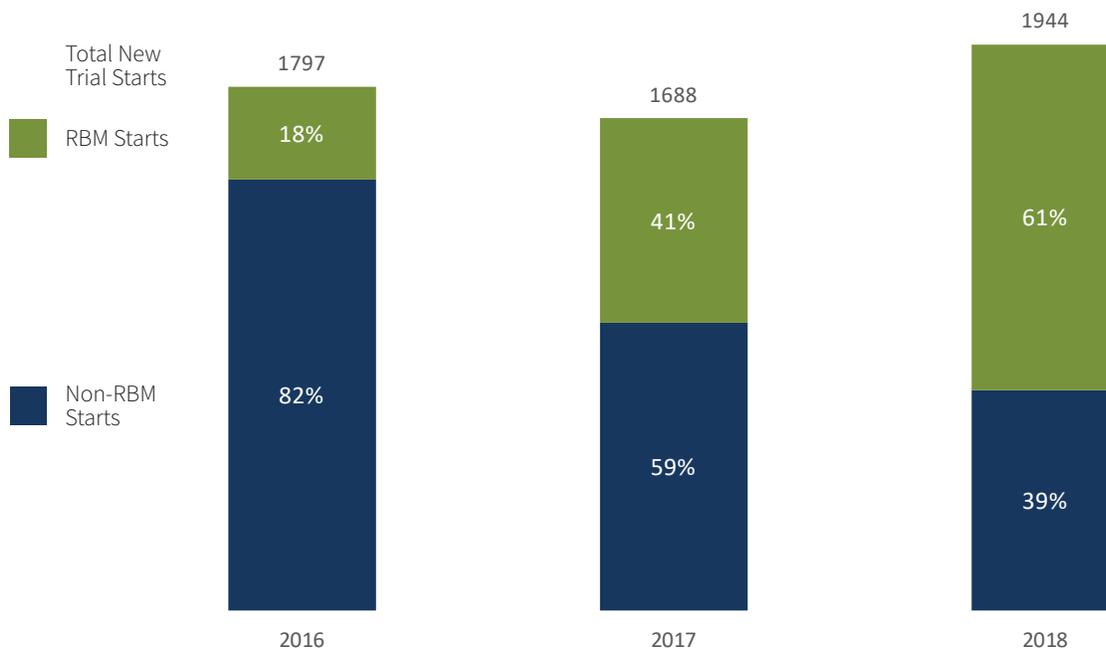
References

1. US Department of Health and Human Services, Food and Drug Administration. *Guidance for Industry: Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring*. Washington, DC: US Department of Health and Human Services; August 2013. OMB Control No. 0910-0733

THE RISK-BASED MONITORING LANDSCAPE IN 2019

In 2019, the Association of Clinical Research Organizations (ACRO) surveyed its members on Risk-Based Monitoring (RBM) processes and implementation.

RBM-ENABLED NEW TRIAL STARTS ARE GROWING AS A PROPORTION OF TOTAL STARTS



In 2016, new trial starts using RBM technology comprised 18% of all starts. That proportion has risen to 61% as of 2018.

Definition of RBM in Survey: “Risk-Based Monitoring: An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality.”

Source: TransCelerate BioPharma Inc. (2017). Section 5 The Next Frontier of RBM - Glossary: Key Terms Defined

<https://www.transceleratebiopharmainc.com/rbminteractiveguide/the-next-frontier-of-rbm/glossary-key-terms-defined/>

CROs ARE INVESTING IN AN RBM-ENABLED FUTURE

Over the last 3-5 years, **ALL ACRO member companies** have made significant investments to advance RBM:

- **Workforce** - Reshaping and adding more positions to support the growth of RBM. Members have developed diverse, cross-functional training programs to support new technologies and processes.
- **Technology** - Building in-house software infrastructure and solutions and partnering with technology vendors to enhance RBM offerings. New generations of RBM offerings have built on years of experience.
- **Processes** - New and updated methods to support and improve RBM across clinical research.

ALL ACRO member companies routinely recommend RBM in their contract bids.

RBM IMPLEMENTATION

Examples of RBM trial evaluation metrics reported by ACRO survey respondents

QUALITY IN RBM TRIALS

- Enhanced ability to identify and manage patient eligibility issues, unreported adverse events and protocol deviations, helping to monitor safety risks
- Central data reviews enabled early detection of quality issues, allowing sites to identify data issues and make early corrections
- 16% reduction in critical and major findings in site audits
- 17% better detection of significant deviations
- 4x lower error rate in critical data in a head-to-head comparison of RBM to traditional 100% SDV approach
- 45% reduction in the number of missing pages in RBM trials versus traditional trials

EFFICIENCY AND SPEED IN RBM TRIALS

- 10-day reduction in data management cycle time for a large sponsor implementing a new RBM technology
- A smaller biotech has seen database locks go from 30-60 days from Last Patient Visit (LPV) to about 5 days
- 40% faster database lock timeline compared to non-RBM trials
- 20% reduction in SDV, resulting in more than \$1M savings for a mid-sized sponsor in the first year
- 3-15% savings over traditional monitoring, depending upon the level of SDR/SDV included
- 21% reduction in subject visit data entry lag

CHALLENGES

Despite the increasing use of RBM, ACRO member companies report challenges that limit wider adoption

PERCEPTION MANAGEMENT

When sponsors request 100% SDV, it is often due to their comfort level with traditional oversight methods and the perception that 100% SDV is the only way to ensure data quality, and thus a “lower risk” market application.

Emerging biopharmaceutical companies with limited portfolios tend to be the most reluctant, choosing what they see as a “safer” strategy of “checking” every data point.

Sponsors perceive audit and inspection findings at research sites, with findings for non-critical discrepancies, as further support for 100% SDV.

Sponsors may also request RBM initially, but then identify additional data points as critical, resulting in little reduction in SDV.

EXPECTATION MANAGEMENT

Non-directive guidance creates varied performance expectations regarding RBM implementation (eg. reduced SDV/SDR) by sponsors, CROs and research sites.

Varied interpretations of ICH E6 (R2) requirements relating to RBM and quality tolerance limits (QTL), creates variability in inspection findings.

Variability in inspection findings creates variability in stakeholder incentives – positive and negative – to implement RBM.

RBM implementation requires consistent and ongoing investment in change management by all parties, including regulators, sponsors, CROs and investigative sites.

ACRO Members

Bioclinica, Covance, ERT, ICON, IQVIA, Medidata, Oracle, PAREXEL, PPD, PRA Health Sciences, Syneos Health