SUMMARY REPORT FROM THE SPRING 2019 EXECUTIVE ROUNDTABLE ON COMPANY RESPONSE TO ICH E6 (R2)

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Introduction

The Tufts Center for the Study of Drug Development (CSDD) facilitated a second executive roundtable with R&D leaders from biopharmaceutical companies to gather experiences and insights on industry response to the International Council for Harmonization's (ICH) addendum to the ICH E6 Guideline for Good Clinical Practice (ICH E6 R2).

A 2017 roundtable found that companies were in the early stages of interpreting the guidance, establishing risk assessment procedures and identifying operating practices impacted. Roundtable participants indicated that their initial focus was largely on risk-based monitoring (RBM). In the 2019 roundtable, companies reported that they have made significant progress in responding to the ICH E6 addendum. Company thinking has evolved and matured and many organizations have incorporated a risk-based framework and mindset across end-to-end development continuum including organizational design, technology use, development execution, training, data management and analytics. What follows is a report on the key takeaways from the 2019 executive roundtable.

Approaches to Risk Assessment Processes

A core theme of the 2019 roundtable is that the ICH E6 R2 (R2) addendum has impacted all functions supporting development activity – requiring risk assessment across the drug development continuum (e.g., planning and design; execution; data quality and management; project program and portfolio decision-making).

Since the introduction of the addendum in 2016, R&D organizations continue to find difficulty in designing and implementing processes to integrate the R2 concepts. Roundtable participants emphasized the critical need to create a strong interface between a proactive quality planning process and a risk-based monitoring process to anticipate risks and performance issues.

An effective study planning process is predicated on developing risk profiles based on historical evidence - a challenge many sponsors with strategic CRO relationships find problematic. Traditional sponsor-CRO collaborative agreements have prevented some sponsor companies from compiling comprehensive longitudinal operating data internally. As a result, many companies have modified their collaborative agreements and/or are focused on capturing and accessing their clinical and operational data assets.

Biopharmaceutical companies widely agree that risk-based approaches have required process and infrastructure change. Specifically, companies have developed quality and risk plans that are defined at the program level and are reassessed at the protocol level. Biopharmaceutical companies note that technologies have been implemented to establish audit trails of risks, how they are managed and reported. Participating companies also indicated that they are developing portfolio-wide reporting systems that characterize trends and provide summaries for senior leadership.

Some biopharmaceutical companies noted that they have implemented RBM pilot studies to develop risk mitigation plans for their investigative sites, set key risk indicators (KRIs) and establish threshold levels to aid in decision-making and data quality.

The ICH E6 R2 addendum has introduced opportunities and implications for vendor, CRO, and subcontractor oversight metrics. Sponsor companies report that they are looking to metrics and sophisticated (and predictive) analytics to improve and optimize performance and protect against the factors that challenge research quality and integrity.

Participant discussion also noted that certain elements of risk management pose challenges that vary among organizations. Company size plays a factor in implementation given variances in available resources and organizational goals. Additional suggestions for implementing an end-to-end risk management strategy:

- Having a holistic view of R2 concepts rather than a segmented approach
- Allowing ample time to train staff on understanding R2 components and RBM systems
- Determining the difference between protocol complexity and risk (complexity to the site, not necessarily of the protocol)
- Retrospective analysis of past site performance, and communicating learnings internally and with investigators
- Encouraging senior management to prioritize all R2 components to produce solutions
- Understanding that data quality is NOT data integrity

Risk-Based Monitoring & Digital Technology

Participants agree that technology solutions are essential to enabling a risk-based approach informed by objective data interrogation routinely conducted. 'Intelligent Data Surveillance and Oversight' allows sponsors and CROs to do what they do best by supporting critical thinking to make the right decisions at the right time for patient safety and improve data quality and overall trial success.

Roundtable participants commented that regulatory agencies are looking for affirmation that companies are using risk-based approaches to streamline development activity. During the roundtable, participants shared anecdotal evidence that the agencies now perceive 100% source data verification (SDV) as a red flag indicator that a risk-based approach was not deployed raising the possibility of an inspection.

R2 appears to have compelled companies to move away from a CRA-centric, site visit model of monitoring to a more data-driven, statistical approach. To find the right tools, larger biopharmaceutical companies may need to revise their internal business structure through multiple transformations, while a smaller organization may only require modest change. For sponsor companies that rely heavily on outsourcing to support a large volume of development activity, it may be difficult to implement oversight & QMS due to limited control over the clinical trial data captured in real time. To gain greater control of, and access to the data, these sponsors may consider moving some or all systems elements in-house (e.g., onsite monitoring and remote monitoring completed by CROs and a quality lead team overseeing study teams so that processes can be done more efficiently and effectively).

Many companies are currently exploring customized solutions for ensuring Good Clinical Practice (GCP) compliance. In conducting risk assessments, roundtable participants report implementing a number of practices including:

- Utilizing data quality oversight tools
- Using advanced and predictive data cleaning
- Moving from data listings to "Data Review Dashboards" to identify trends and data anomalies
- Using advanced data visualization to automatically detect trends and anomalies
- Leveraging automated query management – serious adverse events (SAE) reconciliation
- Conducting supervised self-corrections / action data cleaning oversight
- Using strong quality management systems through effective controls and RBM
- Testing processes and technology integration with current data collection systems/databases (e.g. CTMS, CDMS)

Optimized Study Design and Oversight

Study optimization is a natural progression of the use of analytics to predict outcomes. Participating companies are making significant investments in predictive analytics capabilities that apply not only to risk-based monitoring and predictive vendor/CRO oversight but also to operational outcomes including patient enrolment and protocol feasibility. Roundtable companies report anticipating a shift in traditional analytics used in RBM platforms to more sophisticated real-time and predictive analytics.

Roundtable participants agree that data transparency, accessibility and integration between sponsors, CROs and investigative sites is critical for enabling more predictive analytic approaches. One participant discussed connecting data managers with principal investigators to manage data quality, review site monitoring plans, and compare site performance. Systematic, prioritized, risk-based approaches for optimized study design also involves:

- Distinguishing between reliable data and potentially unreliable data
- Protocol execution plans to assist with increasingly complex study designs
- Avoiding unnecessary protocol complexity
- Updating Standard Operating Procedures (SOPs), and establishing some or all of the following:
    - Protocol Specific Monitoring Plan (PSMP)
    - Data Quality Management Plan (DQMP)
    - Data Review Plan (DRP)
    - Scientific Quality Surveillance Plan (SQS)
    - Safety Monitoring Plan (SMP)
- Auditing RBM processes

Predicting Risks & Performance Issues

Participants recognized that Machine Learning, Natural Language Processing and other types of Artificial Intelligence (AI) are expected to play a major role in ensuring a standard approach to the identification of risks and their mitigation. While AI utilization is nascent at this time, participants expect that AI will assist in efficiently identifying areas of risk and guiding stakeholders to the most successful corrective action. Now that the framework of a Risk-Based Approach to manage the entire clinical trial (a move from RBM to what is now known as RBx – a Risk-Based Approach to Study Execution) is widely accepted, a key next step is to better leverage the data through more advanced analytics to make informed decisions and guide critical thinking.

Attendees noted that there has been increasing focus and investment on improving the ability to manage risks, escalate issues, and implement mitigations. Current issue management systems may not be able to organize information in a way to support data mining and to generate specific reports. There is general agreement that the reporting features are critical to permit visibility for senior leadership and to allow for more control in managing risks, issues, and remediation.

Shift in Company Culture and Employee Training

The R2 addendum focuses companies on driving a more adaptive and innovative approach – a concept that has challenged company culture. Transforming organizational culture to fundamentally change the way data are verified, reviewed, analyzed and managed has become one of the cornerstones of many senior leaders' strategies. Strategies discussed in the roundtable included:

- The development of robust change management training, and digital upskilling to integrate new approaches into standard operating practice. Companies cited examples of app-based training for both monitors, study managers, and other trial contributors that can be consumed "on the go" in small increments.
- The establishment of clinical quality teams to examine ICH E6 (R2) requirements in order to leverage the right tools for data quality oversight.
- The development and assignment of subject matter experts to ensure implementation of steps supporting the addendum. Team discussions covered risk identification, reporting and evaluation, cross-functional sharing of risks, and ongoing monitoring of existing risk control measures.
- The results of pilot studies led some companies to develop Integrated Quality Management Plans (IQMP) and others to transition from risk-based *site* monitoring to risk-based *trial* monitoring. Although approaches to RBM varied, all companies learned that successful implementation of R2 requires training all teams in cross functional strategy alignment. Leadership was also said to be paramount for applying any changes to current SOPs.

Roundtable participants generally agreed that the business rationale for R2 is not primarily cost-driven but quality and effectiveness driven. Attendees agreed that while there may be an increase in near-term operating costs, they expect to see substantial cost efficiencies over time. While some companies felt a cultural aversion to change due to both the increasing complexity of clinical trials and having a multidisciplinary approach, many felt that a predictive analytics capability in line with ICH E6 R2 would drive cost and operational efficiency in three to five years.

The Future of ICH E6 (R2)

Although many participants agreed that R2 has increased operating costs, they spoke about long-term benefits including improvement in oversight, earlier detection and mitigation of risk and proactive and predictive decision making. While

some companies are afraid to change due to increasing complexity of clinical trials and highly fragmented, multidisciplinary functional involvement, many companies believe they will be better positioned to drive efficiency and optimize performance within the next three to five years, if they ensure all aspects of the trial are operationally feasible.

Currently, the FDA is looking at revisions for E8 and a proposal will be going through for the next iteration of renovations to E6. The ICH encourages drug development sponsors to partner with regulators, take more innovative risks and amplify their concerns and ideas.

Participants agreed that it will be valuable to collectively discuss and share learnings and insights from experiences supporting ICH E6 R2 compliance. Roundtable participants pledged to continue to share knowledge and experience to promote more efficient and effective risk assessment approaches moving forward.

Background about the Executive Roundtable

On April 3, the Tufts Center for the Study of Drug Development held a second executive roundtable at the PwC offices in Boston, MA. The roundtable invited senior R&D leaders from biopharmaceutical companies to provide real-case sharing and discuss insights on the ICH E6 R2 regulatory guidelines. The executive roundtable was produced and facilitated by Ken Getz, MBA, Research Associate Professor and Yaritza Peña, Research Analyst.

41 participants from a variety of companies and organizations were in attendance including Alkermes, GSK, MCC, Pfizer, Roche-Genentech, Sage Therapeutics, Takeda, and the FDA. The agenda began with a strategic overview and panel discussion on the current state of ICH E6 (R2) compliance, followed with case examples from organizations coordinating and implementing a response, and ended by addressing barriers and discussing the anticipated direction of ICH E6 (R2).

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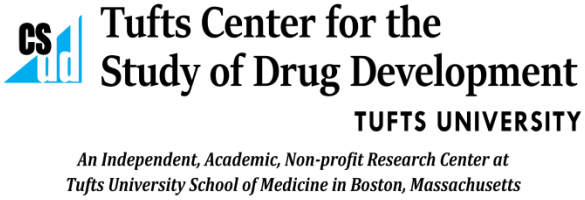
About Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development (Tufts CSDD) is an independent, academic, non-profit research center at Tufts University School of Medicine in Boston, Massachusetts. Our mission is to provide data-driven analysis and strategic insight to help drug developers, regulators, and policy makers improve the quality, efficiency and productivity of pharmaceutical R&D.

Established in 1976, Tufts CSDD conducts scholarly analyses addressing the economic, scientific, political, and legal factors that affect the development and regulation of human therapeutics. For over four decades, Tufts CSDD has been a prominent and influential voice in national and international debates on issues pertaining to biomedical innovation and the development of drugs and biologics. In addition, the Center hosts symposia, workshops, courses, and public forums on related topics, and publishes the Tufts CSDD Impact Report, a bimonthly newsletter providing analysis and insight to critical drug development issues.



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