Tufts Center for the Study of Drug Development
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# Summary of themes from the 2021 Executive Roundtable Examining Experiences Implementing and Accommodating the ICH E6 (R2) Guidance

Tufts Center for the Study of Drug Development, Tufts University School of Medicine | Boston, MA

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# Introduction

On May 2021, the Tufts Center for the Study of Drug Development — in collaboration with, and with funding from, CluePoints and PwC — hosted a virtual roundtable comprised of R&D senior executives from pharmaceutical and biotechnology companies, contract research organizations (CROs) and a representative from the Food and Drug Administration. In total, 60 people participated in a virtual, facilitated discussion.

The purpose of this invitation-only roundtable, third in a series of executive Roundtables convened since 2017, was to candidly examine the ICH E6 R2 Guidance (International Council for Harmonization (ICH) addendum to the ICH E6 Guideline for Good Clinical Practice) to understand:

1. The evolving value and impact of the Guidance; and
2. The challenges associated with implementing practices, procedures and infrastructure to support the Guidance particularly in light of changing operating models, the rising volume of clinical and operating data and the diversity of data sources;

This report presents key themes and insights from the May 2021 roundtable. It is our hope that this report will inform discussions around revisions to the Guidance (ICH E6 R3) expected to begin with a partial release in late 2021.

# Themes on the Current State of ICH E6 R2 Implementations

- There was clear recognition of the conceptual importance of ICH E6 R2 as evidenced by a robust, lively and engaged discussion. Nearly all participants from the 2019 roundtable joined the 2021 roundtable.
- Participants cited a wide variety of implementation experiences across companies. Many commented on how far apart early innovators are from the majority. Since the first roundtable on ICH E6 R2, the most progressive innovators have made significant investments in internal data science functions focused specifically on operational oversight.

- Participants highlighted key factors contributing to the lack of uniformity in industry-wide progress:
    - Difficulty changing company culture and mindset is a recurring theme;
    - Wide variation between companies regarding translation of the Guidance into operating practice with a large proportion of companies still thinking of risk-based monitoring (RBM) as the primary focus of the Guidance (and not Risk-Based Quality Management (RBQM);
    - Quantifying and publicizing the value proposition of ICH E6 R2 (i.e. economic, safety, quality, etc.); and
    - Growing concern about the diversity of data sources (e.g., from EHRs, wearable devices and mobile applications) now supporting clinical study databases — facilitated by the rapid adoption of DCTs during the pandemic — and the challenges associated with coordinating and integrating these data sources to inform oversight and quality management.
- Implementation progress is mostly found among the largest companies – those that have dedicated teams and have made substantial investments.
- Several participants noted that implementation progress within their organizations has been more a function of the charisma and vision of individuals – 'RBQM champions' and less by broad consensus of value and competitive advantage.
- Others reiterated that the Guidance is not "one size fits all." Rather, the implementation of risk management elements present varying levels of difficulty for companies based on size, capacity, available resources, infrastructure and organizational leadership. As such, companies have had to prioritize implementation elements resulting in disproportionately high focus on RBM.
- Although participants are hopeful that the new R3 Guidance may provide clarification, most agree that the Guidance alone is not sufficient to drive more extensive adoption. All agreed that presentations and publications on actual case examples demonstrating implementation experience and quantifying return on investment (ROI) will be invaluable in stimulating and guiding adoption.

## Themes on the Current State of ICH E6 R2 Implementations

- Overall, participants agreed that the Guidance has left substantial room for interpretation with regards to practices, procedures and systems required to support compliance and noted that this has contributed to the wide variation in adoption.

- Several remarked that growing and deeper reliance on outsourcing has also facilitated confusion around which risk management approach — sponsor or CRO — should be used.

- Roundtable participants also noted that regulators have sent mixed messages to sponsor companies — most notably when regulatory inspections rigidly follow old quality oversight models and not RBQM-enhanced approaches.

- Participants suggested that regulators focus more attention on inspection audit trails and results to inform reforming the inspection process to accommodate RBQM.

- Participants expressed concerns that sponsors and regulators may not be aligned on the definition of RBQM and suggested that clarification in the new Guidance on the expected level of RBQM documentation would be very well received.

## Themes on the Difficulty of Articulating the Value Proposition

- There was unanimous agreement that it is difficult to quantify and measure the value proposition of ICH E6 R2 implementations.

- Cost and time-based measures — e.g., head count reductions; improvement in monitor turnover — are measures used by select companies. Most agree that it is hard to accurately capture cost and time measures given the difficulty in using value estimates based on cost avoidance and time saved when comparing current and highly customized activity to traditional approaches.

- Most agreed that ROI is typically not realized during initial implementation, given the up-front investments required and the length of time to achieve widespread adoption. The transition to EDC was raised as a relevant example to current RBQM adoption, where the full value of EDC took a long time to recognize.

- Companies farthest along in implementing RBQM indicate that it has helped their organization free- up and better allocate personnel, remove non-value-added activities, and put stronger operating controls in place resulting in FDA inspections with fewer findings. One major pharmaceutical company shared that implementing RBM reduced monitor turnover by 25%.

- Based on the roundtable discussion, the value proposition appears to vary by company size with larger companies looking to lower operating costs and improve efficiency; smaller companies looking to drive development speed and achieve faster time to market.

- Participants widely agreed that the drug development enterprise needs to publicly share and widely publish actual case examples with hard ROI metrics to help amplify the value proposition; Much of what is published today focuses on frameworks and tips and pointers but not on actual experience and measurable impact.

- Several noted that there are mixed perceptions – and misperceptions -- about the cost of RBM. Most agreed that published case examples will help shape more realistic expectations and consensus.

## Themes on the Challenge of Changing Company Culture

- There was unanimous agreement that changing company culture represents a major barrier to the adoption of principles, practices and approaches supporting RBQM. Participants noted that comprehensive RBQM implementation represents transformative change that many companies, for a variety of reasons, have delayed embracing.

- Select participants discussed ways that they are facilitating culture change:

    - Offering training and digital up-skilling of personnel;

    - Establishing quality teams to identify and prioritize implementation;

    - Creating Guidance experts and ambassadors within companies to help shape senior leadership perspectives, inform cross-functional implementation and share experiences.

## Themes on the Uncertainty and Opportunity of DCTs on Data Integrity, Risk and Oversight

- Roundtable participants largely agree that DCTs represent an opportunity for the drug development enterprise to improve data integrity.

- There was general consensus that clinical trial risk management principles have not changed as a result of adapting to remote and virtual clinical trial activity during the pandemic. The fundamentals remain despite the different clinical trial approaches that have been deployed.

- Participants shared the view that RBQM will achieve higher levels of adoption faster as a result of virtual and remote activity during the pandemic.

- Several noted that there is no longer a single monitor 'role' involved in a clinical trial, but rather multiple individuals — in more extensive internal and external collaboration models — contributing to the 'activity' of monitoring.

- Roundtable participants suggested that the pandemic abruptly eliminated the need for onsite monitoring and elevated awareness of the patient as a new oversight partner. Several companies suggested that they are considering training patients in basic oversight and research integrity principles.

    - One participant expressed her hope that the ICH E6 R3 Guidance will include recognition of the patient (and the caregiver) as a critical data collection and oversight partner in study designs and clinical trial execution plans

- Participants reminded roundtable attendees that there are many mobile and remote assessment technology solutions that have not been sufficiently validated and that validation is essential to ensuring data integrity and the viability of RBQM.

- Participants noted that although DCT usage and clinical data volume are growing, there are two major nascent areas that need to improve significantly to best leverage RBQM: structured and unstructured data integration and the use of machine-learning.

- Apprehension was expressed during the discussion about the volume of data generated by hybrid and DCT activity and the substantial incremental burden this represents for study staff and the increased potential for data errors. Most agreed that RBQM — supported by more sophisticated analytics including artificial intelligence — will be essential.

## ABOUT the Roundtable Hosts: Tufts CSDD, CLUEPOINTS and PWC:

**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.Established in 1976, Tufts CSDD conducts scholarly, globally-oriented research studies to provide data-driven analysis and strategic insights to help drug developers, regulators, and policy makers improve the quality, efficiency and productivity of pharmaceutical R&D. Every year Tufts CSDD also hosts symposia, roundtables, workshops, courses, and public forums to discuss and share ideas and insights on critical drug development issues.

**CluePoints** provides solutions for sponsors and CROs to identify, visualize, manage, and document trial risks that could compromise patient safety and delay the approval of investigational products. Underpinned by Central Statistical Monitoring, a technique that's currently being investigated by the Food and Drug Administration (FDA) for selecting sites for inspection, CluePoints cloud-based products are deployed to support traditional onsite monitoring, medical review and quality to drive a Risk-Based Approach to Study Execution (RBx) and ultimately, to achieve ICH E6 (R2) compliance.

**PwC Pharma & Life Sciences R&D Services** business focuses on delivering transformative models in ClinOps and other R&D functions that drive data-driven decision-making, execution, and oversight for sponsors and CROs. As the industry continues to focus on productivity and speed while managing diversity, quality, safety, and regulatory requirements, PwC solutions have been fit-for-purpose leveraging cutting edge data solutions and technologies focused on outcomes for its clients.