Advanced Clinical

WHITE PAPER

Implementing ICH E6 (R2) and Planning for E6 (R3): Lessons Learned from a CRO Perspective

Kimberly Wanick
Executive Director, Compliance and Quality at Advanced Clinical

Stacy Newalu
Associate Director, Compliance and Quality at Advanced Clinical

Introduction

The R2 update to the International Council for Harmonization Guideline for Good Clinical Practice (ICH E6 R2) included the most significant changes in requirements for clinical trials seen in two decades since its inception in 1996, particularly regarding quality management systems, where a requirement for proactive risk management was added.

Additionally, E6 (R2) expanded sponsor oversight responsibilities to include the requirement for sponsors to implement an end-to-end risk-based monitoring approach across all aspects of clinical research to assess trends, identify gaps, isolate outlier data, and plan appropriate mitigations to address the issues.

The impacts of E6 (R2) on sponsors and CROs included:

- Changes to culture and technology in clinical trial conduct
- Movement toward Quality Risk Management (QRM) throughout the trial lifecycle
- Emphasis on risk-based approaches, design efficiencies, and better use of technology for risk identification
- Acknowledgement of the benefits of using on-site AND centralized monitoring in combination
- Recommendation that clinical trials and data to be clear, concise, and consistent, involving quality and risk management throughout the lifecycle, using technology and methods to increase efficiencies, and focusing on the areas that matter most (risk assessments).

This white paper describes lessons learned during the organizational implementation of E6 (R2) at Advanced Clinical, a mid-market Contract Research Organization (CRO), examining operational hurdles and solutions, examples of how E6 R2 was implemented in active clinical studies, and the resulting QRM structure and auxiliary processes. The paper will also consider takeaways from this experience that can be applied during future regulatory updates such as E6 (R3).

The size of the Sponsor organization has typically dictated their level of comprehensiveness in the implementation.

Challenges for Small and Mid-Sized Sponsors

Depending on the organizational business model of small and mid-sized pharmaceutical companies, the operational approach to E6 (R2) implementation has varied based on the transfer of regulatory obligations, i.e. fully in-house sourced, fully outsourced, or a hybrid model. The size of the Sponsor organization has typically dictated their level of comprehensiveness in the implementation; larger pharmaceutical companies and CROs were able to employ more extensive resources to initiate a broader approach to implementing E6 R2 while smaller organizations needed to be more strategic with limited resources and in some instances, relied heavily on key partners such as CROs. Some of these smaller and mid-sized biopharma firms (SMBs), where novel and innovative research is occurring, have been slower to make these changes, which puts their research in jeopardy. Specifically, if the SMBs are unable to demonstrate that clinical research processes follow the E6 (R2) principles, the integrity of their data is put into question. Not only do SMBs need to establish a new risk-based quality management organizational approach to clinical research, Sponsors must ensure that processes are established describing formal oversight of vendors and greater research investigator oversight at clinical research sites.

Often, SMBs lack the expertise, infrastructure, processes, and resources to ensure these changes are fully implemented; are unaware of the extent of changes required; or do not start early enough in the organizational establishment on developing an effective risk-based quality management approach. As a result, they are at a higher risk of inspection citations due to incomplete implementation of E6 (R2).

As a CRO, Advanced Clinical needed to ensure that processes were updated to allow flexibility to provide more extensive support to smaller-sized, limited-resourced Sponsors and less support for partners who had more established E6 (R2) infrastructures that were utilized in clinical research activities.

Often, SMBs lack the expertise, infrastructure, processes, and resources to ensure these changes are fully implemented.

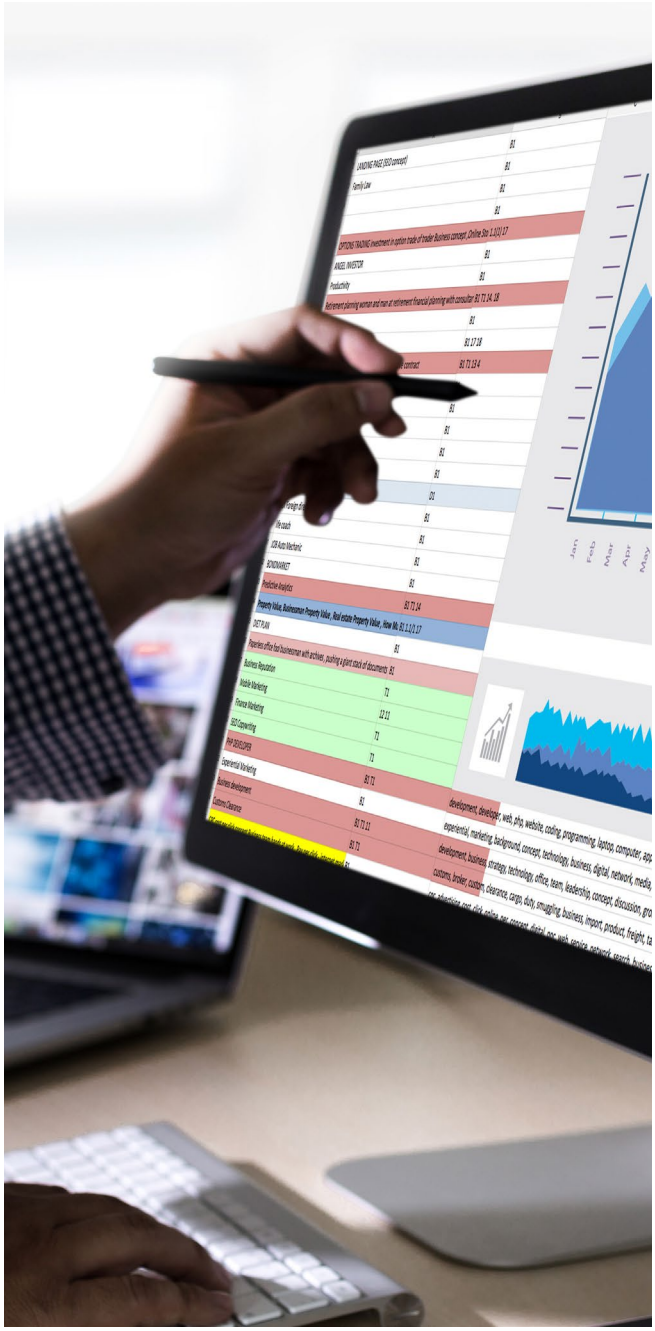
Best Practices for Sponsors and CROs

Prior to implementation, Advanced Clinical educated its clients and gained buy-in on the planned changes and potential impact to ongoing projects, helping to avoid the risk of project delays and non-compliance with the required new processes.

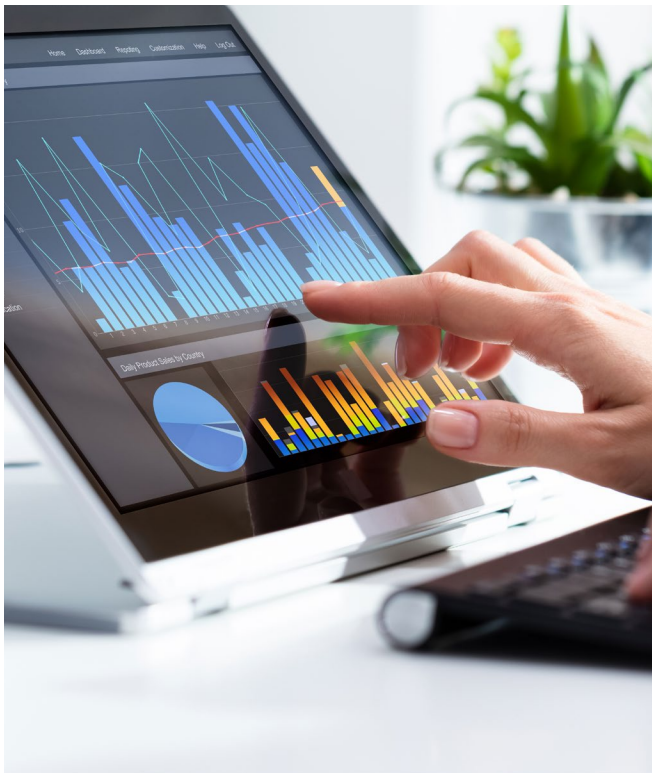
Implementation of such significant process changes often affected all aspects of the current processes (for example, tools such as templates and forms) as well as how various processes interact to ensure changes filter to related processes. Implementation also required engagement of all stakeholders at the earliest possible stages to ensure that the updated and new processes have all relevant buy-in.

Lessons learned related to implementation included the following:

- Initially, Project Managers were challenged to execute all QRM processes (as originally outlined in the applicable SOPs) related to project setup, due to the typical priority tasks such as kick off meeting planning and implementation, project set up, project financial reporting set up, etc.
- Similarly, some sponsors resisted engaging in full QRM implementation, both at project setup timepoint and subsequently during the project, due to other priorities, and they preferred to use their own company's QRM process, incorporating this into CRO study management plans.



- Some sponsor representatives were slow to adopt the regulatory changes due to the novelty of the changes and due to lack of clarity on how the regulatory changes would be evaluated by regulatory authorities.
- Streamlining the CRM process early in the proposal development was a beneficial addition to the previous process.
- Detailed refresher training on operationalizing the CRM process proved to be beneficial within the first year.



Our Experience Indicates That an Effective Implementation Process Requires:

- A project plan including overall strategy
- A gap analysis to identify deficiencies
- An implementation plan detailing what needs to be done and how to achieve this
- Planning meeting(s) with interdepartmental involvement
- QMS updates, including updates on processes and procedures to include the enhancement of the existing project risk log
- Appropriate training – to the general staff population and more detailed to the staff who would be implementing the revised processes
- Efficient launch communication
- Frequent effectiveness checks with adjustments as necessary (e.g., audits of project documentation supporting implementation, process adjustments, management reinforcement and additional staff refresher/re-training as needed)

R2: THE OVERALL APPROACH

The overall goal of E6 (R2) is to guide the industry to use technology where appropriate and pursue innovative approaches.

Encourages:

- Risk-based approaches for quality management and trial oversight
- Focus on critical data and processes (i.e. activities relevant to prove the IP is effective and safe)
- Real-time decision making based via systemic monitoring and oversight

Discourages:

- Paper CRFs/tracking systems
- Collection of unnecessary data

Defines standards/procedures specifically for:

- ALCOAC (Attributable, Legible, Contemporaneous, Original, Accurate, and Complete)
- Computer systems validation
- Management of electronic records and essential documents

Conclusion

An enhancement to the risk log originally updated for the E6 (R2) implementation was key in Advanced's response to COVID-19. Utilization of the risk log, under the temporary planned non-compliance put into place within the early days of the pandemic, allowed for operational flexibility and customization to each project's unique design in real time. The log was invaluable in clearly identifying and documenting COVID specific risks to normal study operations during the initial months of the pandemic that included continuously evolving risk mitigations plans until Advanced formalized a more robust standard set of processes designed to withstand any type of disruption moving forward.

The lessons learned from both the E6 (R2) implementation and COVID 19 response will be helpful with the effort to implement ICH E6 (R3), which is expected by the fall of 2022 per the ich.gov Business Plan. As noted in a final business plan on the ICH website, approved in November 2019, "since the development of E6 (R2), clinical trials have continued to evolve with new designs and technological innovations…E6 (R2) is not fully designed to address emerging technologies, innovations in trial design, the diversity of data sources, testing facilities, and service providers, or to address other emerging complexities of the current clinical trial climate." The business plan states that, "There is also a desire that E6 (R3) should be developed to provide guidance that is applicable to different clinical trial designs and to focus on key principles and objectives. E6 (R2) included a focus on a proportionate, risk-based approach to the design and conduct of clinical trials. E6 (R3) will include R2 concepts that are reorganized, modified, and expanded to further advance diverse approaches to a variety of clinical trial designs and innovative technologies that are adaptable and relevant to our increasing changing clinical research landscape.

References:

[1] https://database.ich.org/sites/default/files/E6-R3_FinalBusinessPlan_2019_1117.pdf

Kimberly Wanick

MS, RQAP-GCP, ASQ-CQA - Executive Director, Compliance and Quality

Kimberly has over 20 years of experience developing and implementing quality infrastructure and SOPs across multiple organizations in various management roles with increasing levels of responsibility. Kimberly has directed, planned, and conducted many audits including sponsor audits, FDA inspections, international health regulatory readiness inspections, ISO 9001:2008 inspections, investigator site audits, TMF audits, for-cause audits, vendor audits, gap assessments, and internal audits. Kimberly holds a Master of Science Degree in Pharmaceutical Science with a Specialization in Drug Development from the University of Cincinnati and a Bachelor of Science Degree in Biological Sciences from Colorado State University.

Stacy Newalu

MPH, RQAP-GCP, CCRC – Associate Director, Compliance and Quality

Stacy has over 20 years of experience in the pharmaceutical industry. She is a former Food and Drug Administration Regulatory Project Manager and has held senior management positions with Human Subject Protections/IRB and outpatient clinical research facilities. Stacy manages contracted Quality Service projects as well as conducts a variety of quality assessments and related activities, including gap assessments, TMF audits, site audits, vendor audits and inspection readiness activities and training. Stacy has extensive experience in creating and managing SOPs, developing and delivering training programs in the areas of research regulations, compliance and quality, and administering and overseeing the regulatory aspects of clinical research. Stacy holds a Master of Public Health Degree in Communicable Diseases, and Bachelor of Science degrees in both Microbiology and Medical Technology.