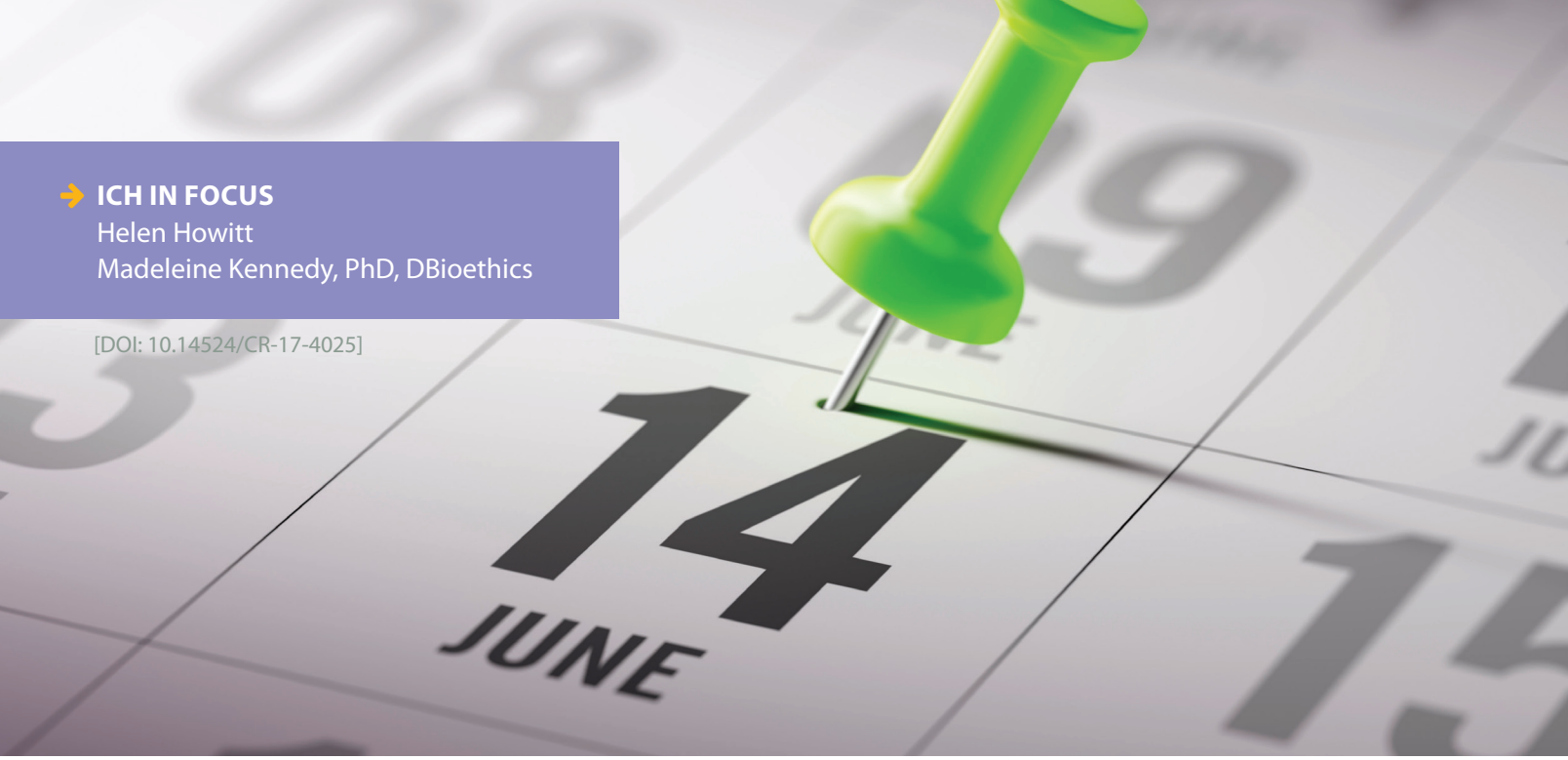

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COUNTDOWN to ICH E6(R2) Implementation

As the implementation date set by the International Council for Harmonization (ICH) for the updated ICH E6(R2) Guideline for Good Clinical Practice (GCP) approaches on June 14, what are the key considerations when assessing your organization's readiness? According to the ICH, the objective of the guideline is to provide "a unified standard for the European Union (EU), Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions."

In this column, which launches an anticipated ongoing series of entries focused on ICH matters in the pages of *Clinical Researcher,* we will explore both the opportunities and the likely challenges ahead, and will suggest ways to meet these challenges.

Background

The release of the ICH E6(R2) GCP addendum (see www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf) marks a milestone in clinical research. It's been 20 years since the release of the first guidance, and there are concerns that, as an industry, we have over-interpreted ICH GCP requirements and failed to maximize opportunities provided by advances in technology during this period.

Indeed, guidance on risk-based monitoring and quality risk management has been available from consortia such as TransCelerate and various regulatory agencies such as the U.S. Food and Drug Administration, European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency in Japan since 2013. So what has stopped the industry from fully adopting the guidance, and what is needed to ensure we fully comply now?

Putting it All in Perspective

Central to the ICH E6(R2) addendum is the requirement to apply a risk-proportionate approach to both the design and execution of clinical trials. No two clinical trials are the same, and not all data within a given trial are of equal importance.

Applying a risk-based approach starts with identifying data and processes that are critical to ensure subject protection and the reliability of trial results during the protocol design phase. Doing so enables the parallel identification of data and processes that would add to the operational complexity without significant impact on the trial outcome.

Next, risks are identified, evaluated, and controlled, taking into consideration whether any identified risks are likely to have a material impact on subject rights and safety, the trial outcome, and regulatory compliance.

Together, the critical data and processes—and the identified, prioritized risks—provide a framework from which the most appropriate monitoring strategy for the trial can be built. This enables

sponsors to determine whether onsite monitoring, a combination of both onsite and centralized monitoring, or only centralized monitoring is appropriate. For example, when evaluating subject eligibility, there may be certain criteria that only the clinical research associate (CRA) may be able to evaluate onsite from the subject's medical records (e.g., details of current concurrent therapies). However, there may be other criteria that can be fully evaluated more quickly and more efficiently through centralized data review (e.g., renal and hepatic functionality based on review of central laboratory results).

Such an approach reduces unnecessary duplication of activities, creating efficiencies whilst ensuring that appropriate monitoring of all data is defined. Documentation of a quality risk management approach and the overarching monitoring strategy in an integrated quality risk management plan provides a framework for detailing and aligning functional monitoring activities.

Risk management is an iterative activity, and throughout the study, the critical data and risks are reviewed for new emerging risks or changes in identified critical data and shared across the study team. In response to any changes, the monitoring strategy is adjusted, thus always ensuring the protection of trial subjects and the robustness of the clinical trial data.

The implementation of these formal quality risk management techniques, combined with advances in technology that enable the surfacing of risks more quickly and effectively, is central to the industry successfully adopting the GCP addendum requirements and modernizing in a way that has failed to happen to date.

Letting Go of the All-or-Nothing Mindset

One of the barriers to success in the past has been a resistance from CRAs to let go of conducting 100% source data verification of all data. By demonstrating through the critical data and process evaluation which data are of most importance, and identifying how best to monitor and review those data during the trial, sponsors can reassure their own staff, site staff, and auditors/regulators that the appropriate control measures are in place to assure subject rights and safety, as well as data integrity.

However, the ability to evaluate data remotely brings its own risks, and must be considered carefully to ensure protection of clinical trial subjects. For example, whilst the evolution of electronic medical records and e-consents may in theory provide the ability to review source data remotely, doing so creates tension with data privacy regulations. In addition, if not well planned and synchronized, the combination of site and centralized monitoring activities could lead to duplicative monitoring and be seen as adding unnecessary administrative burden to investigator sites.

Cultural change management and messaging is also central to the successful implementation of the ICH addendum. It's important to reassure all those concerned (clinical monitoring staff, auditors, and site staff) that taking a risk-based approach is not about cutting costs, transferring more responsibility to investigator sites, or reducing quality or subject safety; rather, it serves to achieve the opposite.

Lastly, it's critical that auditors and regulatory inspectors also adopt a risk-proportionate approach, evaluating the appropriateness of the monitoring strategy applied and compliance with that strategy. If auditors and inspectors continue to check every data point, it may undermine the efforts of the industry to modernize and drive a continued conservative approach to the management of clinical trials.

Recommendations

To summarize, the following five steps are instrumental in achieving compliance with ICH E6(R2), maximizing opportunities, and reducing the challenges that may create a barrier to success:

1. Implement a robust quality risk management methodology, including formal methods to:
   - document and evaluate critical data, processes, and risks;
   - document the rationale for the monitoring strategy and align across all functional areas; and
   - continually monitor changes in risks and critical data or processes and adapt the monitoring strategy accordingly.
2. Develop an overarching integrated quality risk management plan that outlines the proactive risk-based approach for your clinical trial and underpins all other operational plans within your study teams.
3. Encourage transparency and collaboration within your own team and with vendors, other third parties, and investigational site staff. By sharing details of emerging risks, steps can be put in place to minimize their impact, and the most appropriate approach to monitoring the impacted data and/or process can be implemented in a timely manner.
4. Don't underestimate the importance of change management. Developing new processes and tools to support a quality risk management approach is relatively easy; obtaining compliance with those processes and reducing resistance to change takes time and education.
5. Recognize that adoption will take time, there may be unintended consequences, and further change will inevitably come. Technology continues to develop, and as an industry, we need to continually evolve to maximize its use. At the same time, we must always remember that central to everything we do is assuring the safety and privacy of those subjects who agree to participate in our trials and the reliability of the data we collect.

It's been 20 years since the release of the first guidance, and there are concerns that, as an industry, we have over-interpreted ICH GCP requirements and failed to maximize opportunities provided by advances in technology during this period.

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