The Bigger Picture of ICH E6 R2: Looking Beyond Compliance

The introduction of ICH E6 (R2) this past year has rendered the implementation of risk-based monitoring principles a matter of GCP compliance. While clinical research organisations across the industry are now finally compelled to study the new guidance in order to roll out a compliant risk-based monitoring (RBM) strategy, many are still not recognising the incredible opportunity presented by this paradigm shift. And the failure to understand the compelling benefits of an effective RBM implementation will inevitably result in missed opportunity. So instead of viewing the updated ICH guidance as an exercise in compliance, sponsors and CROs need to look beyond simple compliance and towards the transformational improvements they can achieve across their clinical development franchise.

What is the ICH E6 R2 Guideline?

The International Council for Harmonization's (ICH) addendum to the ICH E6 Guideline for Good Clinical Practice (ICH E6 R2) is the first significant update to the GCP guidance in over 20 years. The motivation for this update is summarised in the Introduction section of the updated guideline: "Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased… Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results."

A Crisis in Clinical Development

The first sentence of this summary touches on the significant challenges that our industry has increasingly faced over the past 20 years. Indeed, the complexity of clinical trials – in terms of total number of procedures performed on patients during a study – has risen by more than 50%. Not only has this contributed to higher costs and longer development times, but the additional burden placed on both patients and investigative sites inevitably adds risk to the quality and operational success of clinical research. A review of marketing submissions to the FDA between 2000 and 2012 revealed that nearly one-third (32%) of first-cycle review failures (16% of submissions overall) were failed due to quality issues.[2] Considering the immense investment in time, effort and money needed to take new investigational products through clinical development, this is a startling statistic.

The SDV Debate

The spiralling cost of clinical trials has brought under renewed scrutiny the drivers of this cost. As the single largest driver of cost after investigative site payments, site monitoring contributes up to one-third of the total cost of clinical research globally. The traditional practice of 100% source data verification (SDV) – never dictated in GCP guidelines – drives at least half of total site monitoring effort and therefore up to 15% of the total cost of clinical research.

While the cost implications of comprehensive SDV are high, some may argue that it is a necessary investment to ensure requisite data quality. However, the alarmingly high rate of quality-related submission failures demonstrates that this practice has not been sufficient. And there is growing evidence to confirm that this exhaustive, manual, on-site review process is not only insufficient but ineffective as well. An analysis conducted in 2014 on clinical data from 1168 clinical trials showed that the practice of 100% SDV drives corrections to only 1.1% of site-entered clinical data on average.[3]

The Solution is Here

RBM – along with the concept of quality by design (QBD) – have been strongly endorsed not only in the updated ICH GCP Guidance but in related guidance documents issued by FDA and EMA over the past five years. Both QBD and RBM promise to yield higher quality, shorter timelines and greater operational efficiency in clinical research. QBD and RBM are actually two components of a single paradigm, as both necessitate ongoing assessment and mitigation of operational risk. QBD is conducted at the earliest stages of clinical research design to ensure that studies are optimised not just for scientific merit, but for operational success as well. The concepts of patient-centricity and site-centricity play important roles in this regard. Actively considering the perspective (and plight) of the patient and investigator will lead to study designs that are much more acceptable to both, which should improve enrolment, retention and overall compliance. Once a study protocol has been developed, QBD becomes RBM. Risk assessment is performed on completed designs by a cross-functional study team. Remaining operational risks are identified and prioritised, and risk mitigation and risk monitoring recommendations are established to guide all downstream operational study management plans.

Centralised Statistical Monitoring

ICH E6 (R2) advocates centralised statistical monitoring (CSM) as a core component of operational risk detection, noting that it provides "additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data."[3] CSM is thus positioned as a key to the operational success of any RBM implementation, and for effective oversight of quality in general. CSM uses statistical methods to identify unexpected or unusual patterns in clinical data, and is ideally composed of at least the following three components:

1. **Statistical Data Monitoring (SDM):** This should comprise a well-designed, robust set of statistical tests to be run on all of the clinical data in the study, with the purpose of identifying atypical data patterns that may represent operational risks of various types including fraud, study equipment malfunction, site sloppiness and training issues. SDM as defined here has been very effective at identifying risks that may not have been considered during pre-study risk planning.

2. **Key Risk Indicators (KRIs):** KRIs represent a set of metrics designed to help monitor for known operational risks across all sites in a study. A few examples of commonly-used KRIs include:

- The rate of protocol deviations
- The rate of adverse event reporting
- Timeliness of data entry
- Rates of queries or data errors
- Screen failure rate and early termination rate
- Rate of missed procedures – especially key efficacy or safety procedures

3. **Quality Tolerance Limits (QTLs)**: Similar to KRIs, QTLs represent metrics designed to monitor for specific operational risks. However, the focus is on more systematic issues which, according to ICH E6 (R2), "can impact subject safety or reliability of trial results". While consensus is still developing on the appropriate interpretation of this new ICH language, QTLs should generally be thought of as monitoring for specific thresholds beyond which the study would likely be considered an operational failure.

The combination of SDM, KRIs, and QTLs can provide for a very powerful, comprehensive approach to operational quality and risk monitoring. When designed and implemented effectively, CSM not only drives significantly better quality outcomes, but does so with much greater operational resource efficiency – enabling a significant reduction in the reliance on SDV and related on-monitoring reviews.

Effective CSM does not come automatically. Statistical tests and KRIs that are designed carelessly may lead to a relative inability to identify risks in a timely fashion, and/or a high rate of false risk signalling. This latter issue has too often resulted in unnecessary risk remediation activities which run counter to the actual intent; i.e., more efficient, targeted quality management.

Conclusions

Today, many organisations are still in the process of interpreting the ICH E6 (R2) Guideline to translate the recommendations into tangible operating practices. A risk-based approach to clinical trial management is now a GCP expectation. And while compliance is a legitimate motivator, the principles included should deliver to your organisation much more value than simple compliance:

- Significant reduction in the cost of clinical development, primarily due to the reduced reliance on 100% SDV and frequent on-site monitoring visits.
- Shorter study timelines – driven by improved enrolment and retention rates, as well as more efficient database lock processes.
- Higher marketing approval rates, driven by significantly higher study and data quality.

These should not be considered vague, theoretical or uncertain value propositions. Organisations are already reporting significant cost efficiencies with roll-out of RBM, and many organisations including those belonging to the TransCelerate consortium are observing significant improvements in key quality measures on RBM studies. Now is the time to explore how a change in mindset from simply ensuring compliance towards embracing effective RBM can offer these tremendous business opportunities. The new update has the potential to fundamentally alter how clinical research is managed. Risk-based trial design and quality management will, undoubtedly, be an essential component of the future clinical research landscape for decades to come.

REFERENCES

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