b) Risk-based Clinical Data Management Approaches

Risk-based Clinical Data Management finds its origin in the Risk-Based Monitoring (RBM) FDA guidance and EMA reflection paper and is reinforced by ICH E6 (R2). While the first two are suggesting resource optimization in some of the on-site monitoring activities by adopting a Risk-based approach (e.g. focus on what really matters: critical data and processes), the ICH E6 (R2) is reinforcing and broadening the perspective to better address Data Quality expectations. It is offering an interesting and innovative perspective on how we should be conducting clinical trials by inviting sponsors (and CROs) to consider risk-based study execution to enable operational efficiency.

ICH E6 (R2) starts with a brand-new section dedicated to Risk Identification and Assessment (section 5.0). A mission expected not to be just focused on operational matters but on any aspect of the clinical trial execution that may put the entire submission at risk. As a result, risk controls and risks mitigations are expected to be defined, monitored and documented. CDM is at the core of some of these controls

and mitigations. So, it is essential that CDM contributes to the Risk Identification and Assessment together with the other key study team players.

It is also worth mentioning that the Risk Assessment process may offer an opportunity to help frame and author the cross functional Quality Management Plan (QMP) and most of the other functional plans (e.g., Data Management Plan and Clinical Monitoring Plan). Indeed, as the study team goes through the risks and defines controls and mitigations (together with responsibilities and frequency of actions), it is likely that the outcome of such assessment provides most of the elements that are present in all plans such as the Data Management and Data Review plans. Technologies might help to facilitate the authoring and synchronization of these essential documents and avoid duplication of work while ensuring alignment with the overall QMP.

Across the ICH E6 (R2) guidance, we also see the growing role of data analytics to support the detection of atypical patterns. Sections 5.0.4 and 5.0.7, related to Risk Control and Review, are suggesting the need to use analytical techniques such as Key Risk Indicators (KRIs) and/or Quality Tolerance Limits (QTLs) to measure the risk during the conduct of the trial and detect anomalies. The CRO oversight addition to section 5.2 and the new central monitoring role supported by statistical techniques defined in section 5.18.3 are suggesting that we should go beyond just a "supervised" approach and enlarge the spectrum of data to be monitored. In other words, the risk controls are there to monitor the risks that the study team thought may happen, however their limited number make it impossible to address every possibility. So, even though challenging to implement, an approach where analytics are used to monitor **all collected data** near real time, may help "guarantee" that most if not all issues are detected.

To support these new analytical methods, the study team needs new skills and critical thinking. Skills that likely reside, as indicated in section 5.18.3, in Data Management or Biometrics functions. A new role, the centralized monitor, that complements the site monitor during his/her investigations is also emerging in some companies.