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Examples of Risk-Based Quality Management Practices on Small-Scale Clinical Trials

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Introduction

The concepts of Risk-Based Quality Management (RBQM) in Clinical trials are no longer new to the industry and are well-endorsed by regulatory guidance such as ICH E6 (R2) and ICH E8 (R1). The implementation of RBQM has driven a shift away from relying on traditional quality assurance techniques such as Source Data Verification (SDV). Today we are encouraged to implement more proportional and sensitive quality/issue detection techniques that are based on perceived and actual clinical trial risk. Concepts such as Risk Assessment, Quality Tolerance Limits (QTLs) and Key Risk Indicators (KRIs) are often applied to clinical trials, but sometimes their applicability and appropriateness to smaller clinical trials is not perceived in the same way as they are for larger, multi-centre, multi-region clinical trials. This guide is designed to discuss many of these RBQM concepts and to specifically examine how each concept can support smaller-scale clinical trials.

Firstly, the definition of 'small-scale' is worth expanding on. The types of clinical trial that can apply to this definition are Clinical Trials with very few participating sites, such as in Phase I trials, and/or trials with very few participants, akin to some Rare Disease clinical trials. There are also trials that can have very few sites and participants, such as those used for proving feasibility before extending into full Randomised Clinical Trials that will equally benefit from RBQM practices.

1. Risk Assessment

Risk planning and risk assessment now sit at the heart of regulatory guidance for clinical trials and implementing Critical to Quality factors, critical processes and data, risk identification and risk mitigation planning will deliver value on any clinical trial no matter the size or scale. Just because a trial is of smaller scale, it does not follow that it is not liable to risk that could impact the trial and data integrity or have a negative impact on participant safety. Performing an early risk assessment provides the opportunity to apply quality principles at the outset with the potential to adapt to perceived risk and adapt a clinical protocol appropriately. This could decrease complexity and help a trial to be operationalised in the fast-paced Phase I environment or remove burden from participants who are already hard to find in rare disease situations. Proactively assessing risk and designing quality into a trial early will help with appropriate site selection and is more likely to facilitate successful execution. Where previous experience utilising sites exists, reviewing historical performance is a valuable component of the risk assessment process that can influence re-selection of sites to maximise the chances of successful execution of the trial. Additionally, Risk Assessment should be a 'living' activity, re-assessing the trial for risk after a reasonable duration, or when a new milestone is reached, such as before 'First Patient In' (FPI), to check perception of risk has not changed since the initial risk assessment.

2. Quality Tolerance Limits (QTLs)

Quality Tolerance Limits are metrics with thresholds that, if breached, would indicate the trial was significantly at risk from successful completion and/or a potentially serious patient safety issue has developed. The need for QTLs on any clinical trial is called for in ICH E6 (R2) Section 5. Implementing and monitoring such study-level QTLs should be considered, regardless of size and scale.

3. Key Risk Indicators (KRIs)

Key Risk Indicators have formed the cornerstone of site-based issue detection with the adoption of RBQM but there are diverse ways KRIs can be implemented that may govern their applicability to small-scale clinical trials.

1.> Comparative Site Performance – this type of KRI is more sophisticated as they generate performance results for each site and then communicate how good or bad that performance is by displaying the results against the performance of all sites in the trial. This approach is driven by statistical methods which will want a reasonable volume of site data to deliver results from. For example, if you have a single site Phase I study, comparative site performance results will not be possible.

2.> Site Performance against thresholds – this type of KRI is more simplistic, in that it calculates site performance and displays the results against thresholds that you have specified for the individual KRI. While being more simplistic, they do offer the benefit of being applicable to smaller-scale studies where comparative site performance results are not possible given a small number of sites to compare.

If a trial has a small number of sites that preclude the implementation of Comparative Site Performance KRIs, there is always the opportunity to re-focus the implementation of such KRIs at the patient level and drive a comparative result from the patients rather than by comparing sites. However, for the few sites that do exist, consider implementing site-level KRIs that display against the thresholds you provide, while then implementing KRIs that compare performance at the individual patient level. This means that you can monitor for anomalies in the contributing patient population at the site. In this scenario, the same KRIs are used at the site level and the patient level. At the site level you monitor the KRI against your own thresholds and at the patient-level you see relative results. Setting your own KRI thresholds can pose challenges however, this is because it can be difficult to identify the thresholds you might need for every KRI you want to implement. Some KRIs, such as Data Entry Timeliness, are easy enough to define based on experience or looking back across previous trials. The more protocol specific KRIs you implement might be more difficult to set thresholds for, which is where a Comparative Performance KRIs are so valuable as they will highlight differences in data by comparing actual individual site/patient performance against performance for the rest of the sites/patients within the trial.

There is also the opportunity to deploy study-level KRIs for other important monitoring metrics. The difference here between a study-level KRI and a QTL (also a study-level metric), is that unlike a QTL, a study-level KRI does not need to be reported as part of the Clinical Study Report (CSR) if it becomes breached. Such study-level KRIs will use thresholds set by you, but having historical data to look back on to help set thresholds at the study level is not necessarily easy for everyone, especially smaller organisations with fewer historical trials to pull previous insights from.

The message here however is that KRIs provide multiple approaches for implementation that can fit the nature of the trial and the number of sites participating, so that they are equally able to support the monitoring of a small-scale trial compared with larger, multi-centre examples.

4. Patient-level Insights

Detecting risk at the patient-level can further supplement the KRI approach described above. There are 3 additional ways to discover risks by focusing on patient data directly:

1. When it becomes challenging to implement KRIs at the site-level and use statistically driven comparative results because of a small number of sites, there is always the possibility that there are enough participants in the trial to move such KRIs down to the participant level. KRIs can be implemented and computed by comparing results from one participant to all the participants.

2. Individual Patient Data Reviews using Patient Profile-like solutions. Medical Monitoring, Safety Monitoring, and monitoring of key efficacy results of each patient provide a different lens through which to detect risk in patient data. Being able to easily review any given patient and easily focus on specific data of interest from the patient record, as well as combine data onto the timeline of patient participation so that it is easy to look for correlations in results and study events, delivers easy oversight and patient safety review. The key word here is “easy”! Today there are many instances of patient data review being performed from listings of data which do not provide the easiest, efficient, or most user-friendly approach to perform individual patient review. Implementing this kind of a patient-level review can benefit from more graphical solutions that present results in the form of a Gannt Chart for instance.

3. Professional/Duplicate Patient Detection. There are certain types of clinical trial where participants/volunteers have a motivation to participate in the trial more than once. Be this for financial reward as we know with ‘Professional’ participants in a Phase I scenario, or desire to ensure access to study medication rather than placebo which is known to be a risk in the CNS Therapeutic Area. The ability for a patient to try to enrol themselves again is much more likely in trials that have multiple sites where they would not be remembered, and where investigational sites are geographically close. Having an ability to use collected data to identify duplicate participants to preserve the integrity of data collected and protect the patient from a safety point of view are valuable additions to the monitoring techniques used on a trial. Ideally being able to define the datapoints utilised by duplicate checks will help, as these can differ between trials.

5. Data Visualizations and Aggregate Data Views

When we think about a per-patient data review as described above, a natural extension is to think of specific areas of clinical data that might benefit from review across all the participants in the trial, being able to easily review all results in one place. Examples might be a review of all the Serious Adverse Events, Adverse Events of Special Interest, or looking at Liver Enzyme Lab Parameter results. Using more generic data visualizations that benefit from visual styles well-suited to easy communication of results, such as Scatter Plots, Column/Bar Charts, Line charts etc are a terrific way to get a more holistic review of interesting data across the whole patient population and identify additional risk. As well as helping to identify risk, such visualizations can provide a great supporting tool to help explore the trial data in reaction to some of the other risk detection techniques already documented. With that said, if it is possible to identify a potential risk scenario that really would be fundamental to the success of the trial, it is better to directly target that risk with QTLs or KRIs that will explicitly flag the problem, rather than leaving it to interpretation of data visualisations.

6. Unsupervised Data Surveillance

The techniques for risk detection outlined above have all followed a supervised approach. A supervised approach is where we perceive a potential for risk to de-rail our trial, so we implement a monitoring technique capable of easily showing us if a risk or issue is beginning to surface. With a supervised approach, it is unlikely and unreasonable to expect that our study teams will be able to supervise and monitor every data point in a way that would detect all potential quality and integrity problems. The time and effort involved simply make this impractical. However, technology-based solutions can test all the data collected and test for emergent risk by looking at all data points, even those that have not been classified as critical during the risk assessment/planning activities. Such solutions might work by using statistical interrogation and/or detection of complex data issues from machine learning models trained on historical data. Unsupervised approaches clearly require access to, or investment in, enabling technology. Usually, they can be leveraged on a trial-by-trial basis and do not require a significant investment. An unsupervised approach will complement the supervised approaches documented above and provides the most comprehensive approach to detecting emergent risk from data.

7. Conclusion

All the techniques discussed in this document have been leveraged for Risk-Based Quality Management on clinical trials for many years. When we consider how applicable they might be on small-scale clinical trials, the answer is always that they can absolutely deliver value. The nuance however is in how they are applied to each clinical trial on which they are implemented. Do we shift from a Site-focus to a Patient-focus? Do we rely more on our own thresholds than comparative results with small numbers of sites? Do we blend site-based metrics with patient-focused comparisons? Keeping these concepts in mind can help with the decision making on how best to monitor for and mitigate risks perceived on smaller-scale clinical trials.

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