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Advancing Clinical Research with Risk-based Quality Management (RBQM)

What is RBQM, what are Benefits, Return on Investment, and why it's worth the Effort

The overall focus of Risk-based Quality Management (RBQM) is on the quality of the data generated in clinical trials as well as on patient safety and patient rights. The process of implementation should start with getting an understanding of the overall concept of RBQM and also training on the various related aspects is of high importance. However, the implementation of RBQM comes along with some challenges, to which the author draws attention in the following article. He also addresses the many true benefits one could generate by implementing RBQM.

| Johann Pröve

Introduction

For decades, pharmaceutical, biotech and medical device companies as well as Contract Research Organisations (CROs) trained their various functions on cleaning the clinical trial data as much as possible to ensure acceptance of the data once submitted for approval by the health authorities. In addition, the volume of data collected in a clinical trial has increased drastically over the past decade. While the Case Report Form (CRF)—about 15 years ago—had about 50 to 70 pages per patient, this number has grown up to a full binder of pages to be completed for one single patient in a study. The reason for this growth can be attributed mainly to a change in indications studied e.g. more oncology and long-term trials, and the addition of more and more examinations per patient in order to fully utilise the time a patient spends at the site.

All of the above results in:

- Site monitors spending a lot of time on Source Data Verification (SDV) e.g. comparing the source or patient record data with the data captured on the paper-based CRFs or in the Electronic Data Capture (EDC) system.
- Programmers generating code to check the data in the EDC system or in the backend database management system, in so-called edit checks. The number of those checks has increased to a magnitude of about 1,200 to 1,500 edit checks per study.
- Data managers posting lots of queries related to: backend database management edit checks, medical monitoring and medical coding, the Serious Adverse Events (SAE) reconciliation process between the clinical and the pharmacovigilance databases in the EDC system, and several other sources. In worst case scenarios, spelling errors of medical history findings, adverse events, concomitant medications or other textual data errors in the CRF also resulted in a query, despite the fact that probably 99 per cent

of the spelling errors could have been corrected by the sponsor company without bothering the site staff.
- Site staff trying to catch up with the many queries generated either by the EDC system or provided by the clinical data management organisation of the sponsor company or the CRO.

In summary, the time spent on data cleaning has got out of hand, while the number of queries posted and resulting in actual data changes by the site staff (where the data had indeed been entered incorrectly) was marginal. [1]

In addition, about 25 per cent of the costs related to conducting a clinical study were spent on site monitoring and on SDV.

Unfortunately, despite of all of the above-mentioned efforts, many clinical studies still suffered from poor quality in important areas of the clinical study data, such as:
- Numerous missing primary efficacy data,
- Major protocol deviations above and beyond the acceptable rate,
- SAEs being reported late in the process rather than within 24 hours after becoming known to the site staff,
- Higher than acceptable number of patients "lost to follow up" in outcome studies potentially resulting in non-acceptance by the health authorities,
- Site staff not adhering to the randomisation and the stratification scheme,
- Certain sites being different with respect to the patients enrolled compared to all the other sites,
- Secondary endpoints only collected sporadically and thus not available/useful for any analyses,
- And many other quality issues.

Besides the costs for monitoring, the above issues frequently resulted in either a delay in the availability of the study results, in unrecoverable gaps for the study evaluation, or—worst case—in non-acceptance of the studies and the data by the health authorities.

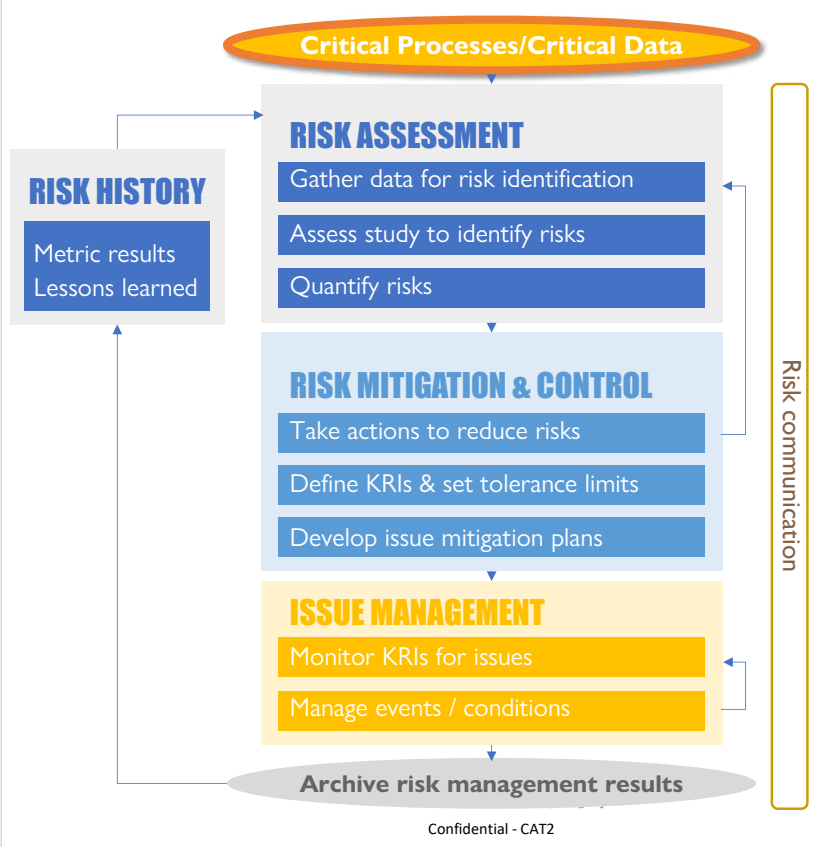

Figure 1: High-level Risk-based Quality Management process.

These issues and concerns about the quality of the clinical studies and the associated costs related to managing studies led to the development of the ICH E6 (R1) guideline between 1996 and 2002 mainly addressing Good Clinical Practice across all its facets. [2] In 2016, an addendum to ICH E6 (R1) was released, a version that is currently still in use by the industry and that addresses the risk-based approach to clinical trial conduct. [3]

These updates raise several questions: What does the process look like? What does this guideline mean for the industry? [4] Who will be affected? What are the benefits? Is it ultimately worth the effort?

The Risk-based Quality Management process

Understanding and training

The process of RBQM implementation should start with getting an understanding of the overall concept of RBQM and training on the various related aspects. This is a prerequisite not different from any other processes that one wants to implement.

Once training has been conducted and a solid understanding of RBQM has been established in an organisation, one should start identifying the responsible individuals or functions to take over a certain role related to RBQM. Such roles could include the risk manager, the central monitor, the RBQM project lead and several other roles that could either be covered by one or more individuals depending on the size of the organisation and the scope of the RBQM rollout.

RBQM could be started by implementing a basic process using a draft protocol or a final protocol and by identifying the critical data and the critical processes (see Figure 1).
- Critical data are usually those that are important for the study, such as the primary efficacy criteria, the in- and exclusion criteria, SAE data, data on dropout and lost to follow-up, and secondary efficacy criteria.

- Critical processes are those related to the generation, capture or management of critical data, such as quality of the images, data entry timelines into an EDC system, adherence to the randomisation and stratification of the patients, or follow-up of patients that were initially categorised as "lost-to-follow-up".
- There may be other critical data and other critical processes that are not necessarily described in a study protocol, such as reporting timelines for SAE, adherence to cooling requirements for lab sample shipments, completeness and quality of monitoring reports, response times to queries, or the number of minor, major or critical protocol deviations.

The critical data and critical processes should be identified by the study team members, maybe with the support of some external functions such as pharmacovigilance, pharmacokinetics or bio-analytics, depending on the requirements of a protocol. This, unfortunately, frequently does not happen. [5]

The risk assessment

In a second step, the study team should be working on the risk assessment. This process should start with a brainstorming session on the potential risks associated with the critical data and the critical processes, however, also consider all other potential risks related to the study, with the focus on the data quality/integrity, the patients' safety and the patients' rights.

- Risks should be listed and potentially categorised by e.g. safety related, data management related, blinding related, complexity related, etc.
  - see also [4]
- Risks should be scored with respect to their likelihood of occurrence, their impact on the study outcome and their detectability, in order to e.g. intervene in time to correct a process.
- Risks should ultimately be categorised as "acceptable" (if the score is low enough) or as "mitigate" (if the score is high).
- The final list should have about 10 to a maximum of 25 risks that a sponsor company wants to keep under control.

The above process will ensure that all critical data and critical processes for a study will be managed properly, and no surprises will come about in the most important data and processes.

Risk mitigation and risk control

The next step in the process is the risk mitigation and risk control step. In order to be able to manage the risks one has to implement mitigation actions. Mitigation actions can already be implemented at the protocol design stage e.g. remove superfluous examinations, reduce the complexity of the protocol, use central labs instead of local labs, and other similar mitigations. One could also ensure that site staff is thoroughly trained on the tests, examinations and data capture processes required by the protocol, thus preventing any issues early on.

The most difficult area in the RBQM implementation process is often the definition of Key Risk Indicators (KRIs). KRIs are metrics with a certain threshold (or even two thresholds) that create an alert once the thresholds have been breached, indicating that a critical data point or a critical process is out of control. The KRI thresholds should be set such that it is still possible to initiate a mitigation action and get the risk under control before any serious impact occurs; however, they should also not be too sensitive in that the KRI constantly creates an alert.

In preparation for the study conduct, an issue mitigation plan must be established. Such a plan indicates who should be alerted if a KRI creates a signal, who is accountable for the follow-up, what kind of mitigation actions should be triggered, and whether or not a KRI threshold

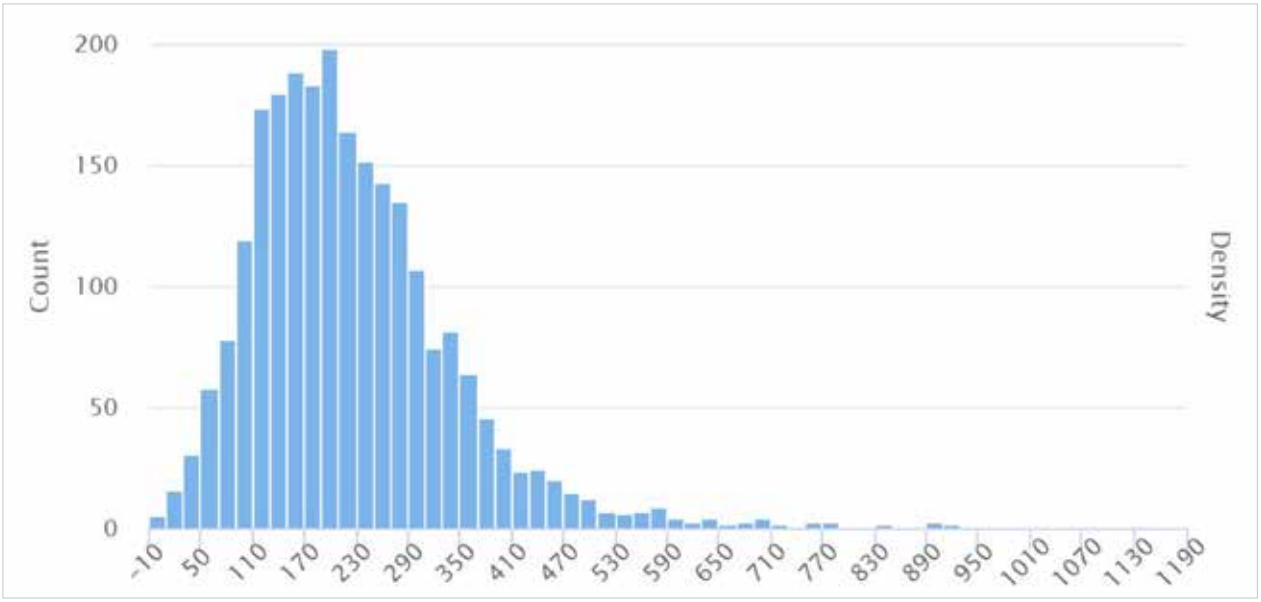

Figure 2: Platelet data distribution using a histogram.

breach should be followed up via a Root Cause Analysis process or even a Corrective Action & Preventive Action (CAPA) process.

The moment that the first patient gets enrolled, someone—for example a central monitor—must monitor the RBQM system, if applicable and installed, for any issues that may surface. Commonly, few KRIs will generate a signal based on the first subject data, however, with an increasing number of patients in the study, the likelihood that something may go wrong in the study increases. Preferably, a central monitor will review the system regularly (the frequency depends on the enrollment and the number of visits per subject) and decide whether to accept a breach of a KRI threshold as inconsequential, or whether to initiate a mitigation action to limit the impact of a realised risk.

Despite the pre-defined risks, metrics and KRIs, other potential problems in the data may remain undetected. Here, using a centralised statistical monitoring system and process may also help in identifying those additional risk areas that originally had not been viewed as potentially risky. A centralised statistical monitoring system should have access to all (numeric) data in a study and creates—depending on the system—a graphical view of the data, such as a histogram of the data distribution, a scatter plot showing data dependencies, box plots of the data and any other helpful visualisations of the data of interest.

This analysis of the data and subsequent review of the graphical outputs may result in the discovery of other risks, which need to be added to the risk catalog or library. In the example presented in Figure 2, one may decide to set up an alert (KRI) once a platelet value exceeds 600 Giga/Liter.

Once a KRI breach triggers an alert that needs to be managed e.g. an issue has surfaced, mitigation actions should be initiated. These mitigation actions could be triggered…

- on a study level, if a risk for an entire study is materialising, for example due to many more SAEs reported than expected, or
- on a country level, if a risk surfaces for a particular country e.g. due to many protocol violations in a country based on use of non-permitted drugs, or
- on a site level, if a site obviously generates data jeopardising the study, or even
- on a patient level, if a particular patient stands out from the rest of the patient population.

Examples of mitigation actions may be e.g. intensified site monitoring visits, re-training of the site staff, provision of laminated cards with instructions, or any other hand-holding activities for the site staff. The ultimate objective of the mitigation actions is to get the KRI level back into the design space respectively into the acceptable area again.

The effect of the implementation of mitigation actions has to be reviewed on an ongoing basis and a decision must be made on whether or not it is necessary to kick off additional mitigation actions in order to get the quality of the data, the patient safety, or the adherence of the patient rights under control again.

In some cases, depending on the seriousness of the KRI breaches, an organisation may decide to trigger a CAPA process since the issue is so serious.

At the end of a study, the lessons learned during the study should be archived and used as the basis for the next study. It is also advisable to share the lessons learned with other study teams currently planning a new study or working on an ongoing study, particularly those in similar therapeutic areas, indications or compounds.

The complexities

Initiating the introduction of RBQM comes along with some challenges, in some cases similar to the implementation of other processes and systems.

The first challenge is that there is only limited experience available in the industry of the use of RBQM. Is it the best approach to start small, with just one or two studies, or use the big bang approach e.g. after 1 january all studies will be using the new technology and the new processes? It is recommended to start with a retrospective analysis e.g. completing an RBQM approach on a completed study, to see what works well and what may still need some tweaking, process wise and training wise.

The second challenge is the selection of the preferred approach with respect to technology. Is it sufficient to use Excel and what may be the limitations of Excel? A spreadsheet may be helpful in collecting the risks and run the scoring of the risks; however, the moment a link to the study data is required, Excel does not work anymore. Does one want to use the TransCelerate proposed approach [4] or the one suggested by Metrics Champions Consortium (MCC)? [6] Long-term, and when considering the link of the risks and KRIs with the data of a study, it is advisable to use an off-the-shelf RBQM system.

Thirdly, one has to decide whether to implement a Risk-based Monitoring (RBM) tool or go further and implement a Risk-based Quality Management (RBQM) tool. The latter has the beauty of also managing other risks than just those related to monitoring, such as central labs not delivering according to the expectation, electronic Trial Maser File (eTMF) files not being maintained in the required quality, or not having a centralised statistical monitoring functionality in place. Thus, it is certainly advisable to implement an RBQM tool and the related processes.

Fourthly, it seems to be rather difficult to focus on the critical data and the critical processes (or what will likely be called Critical to Quality Factors—CTQs—in ICH E6 (R3) [7]). Prior to finalising the protocol for a new study, one should

consider whether all the visits and examinations are necessary to capture sufficient information about the efficacy and safety properties of the compound under investigation. Is it necessary to have the patients complete a set of five different questionnaires or would it suffice to have them complete just three? Is it necessary to have seven eye examinations in the protocol while the primary efficacy parameter is whether or not the patient can read smaller letters at the end of the study compared to the start of the study? If a protocol can be simplified and streamlined, the number of potential risks will also decrease.

Fifthly, one must consider all the various data sources required to run RBQM. Are the risks only in the data captured in the EDC system or are other data sources also part of the risk library? Since the risks may be based on data originating from different data capture or data storage systems, RBQM must tap into those different systems in order to run the respective analyses on those data. Those other data sources can be the Clinical Trial Management System (CTMS), the Drug Safety System, the Clinical Database Management System (CDMS), the Interactive X Randomisation System (IXRS), the electronic Patient Reported Outcome (ePRO) system, or any other system holding clinical trial data.

Finally, one must not forget about the people. Many companies train their staff on the importance of absolutely clean clinical trial data by performing 100 per cent SDV, by implementing thousands of edit checks into the EDC system and by re-checking everything that had been done a second time. Now, with the implementation of RBQM, site monitors do not have to check every data point 100 per cent, nor is data management required to build edit checks for each and every data point in the database. Instead, critical data and processes are being identified and those are being checked by a risk-based approach. To transition an entire organisation from the past processes to the new way of working, dedicated and specific training modules have to be developed and delivered to the clinical operations functions. Fortunately, those training modules are available, on a rather generic basis or also on a customised basis depending on the needs of a company.

Examples

What are typical questions related to the benefits of an RBQM implementation? Usually, one probably wants to get answers on the following questions:

1. Which risks manifested themselves during the study?
2. When would it have been possible to already identify a risky situation?
3. At which point in time could they have been counteracted?
4. Which risk defense strategy suits this study? How could this information be used best in the future?
5. Which dynamics could be expected for similar studies?
6. Which KRIs worked the best and should they be accepted as corporate standards?

1. What risks manifested themselves during the study?

Generally, SAEs in a long-term study should have been at a similar level at the participating hospitals. In one example, one site substantially exceeded the expected number of SAEs per visit and did so throughout the course of the study (Figure 3, red line). The risk materialised itself already early on in the study and one could have checked why this site performed so differently compared to the average SAEs per visit for all the other sites (green area).

2./3. When would it have been possible to already identify a risky situation? At which point in time could they have been counteracted?

Outcome studies usually require that not too many patients are lost-to-follow up e.g. the outcome is unknown. In the case below (Figure 4—an example from a retrospective analysis), more and more patients were lost-to-follow up. In a case where one had seen this trend already in autumn 2018 and one had implemented mitigation actions to prevent such a development from happening, the lost to follow up rate could likely have been controlled and kept under the acceptable 2 per cent threshold.

4. Which risk defense strategy suits this study? How could this information be used best in the future?

It is important to understand whether the mitigation actions implemented improved the risk and drove the KRI back into the design space/the acceptable range. A high number of protocol deviations per patient may be a risk for a study and thus, the number needs to be con-

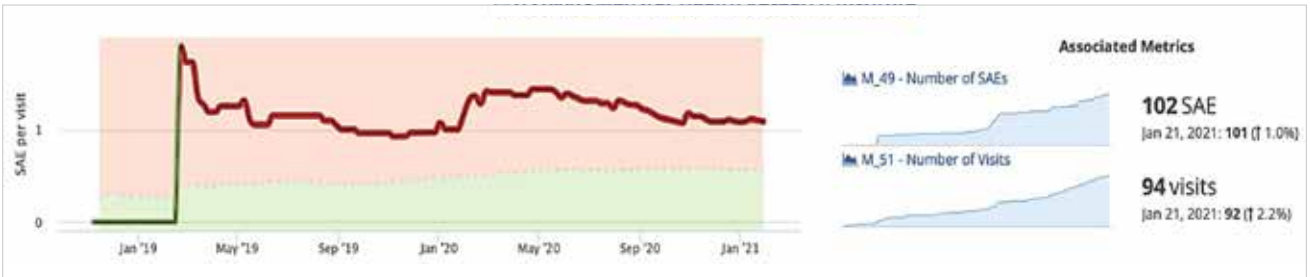

Figure 3: Serious Adverse Events per patient visit for one site in a study.

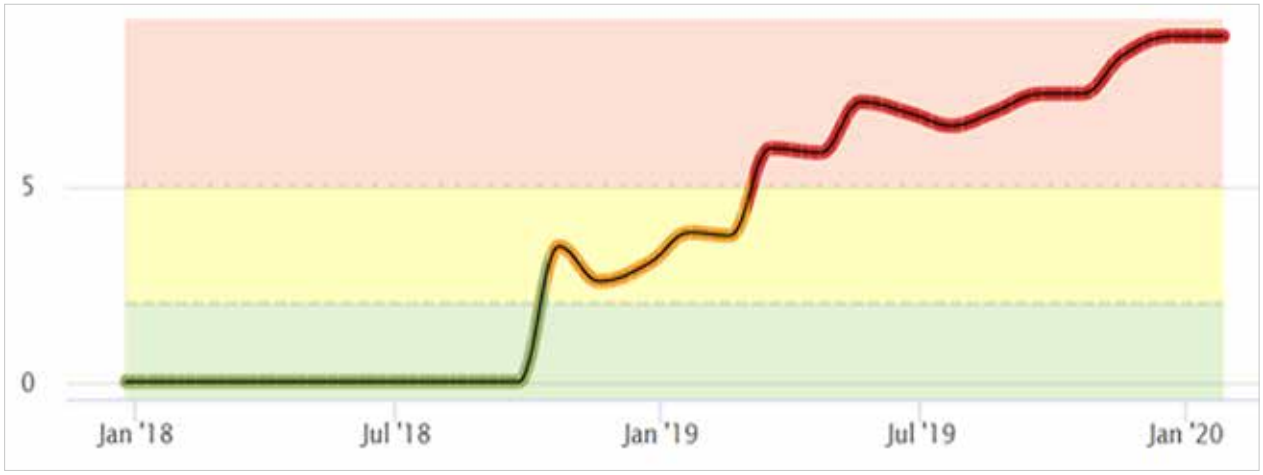

Figure 4: Number of patients lost to follow up (per cent of all patients randomized)

trolled thoroughly. In the example below (Figure 5), the sites started off by not adhering to the protocol as expected (December 2018). After a monitoring visit (February 2019) and explanation of the importance of protocol adherence, the situation improved.

5. Which dynamics could be expected for similar studies?

For many indications, a submission to the U.S. American Food and Drug Administration (FDA) requires two pivotal phase 3 studies to be submitted. That usually results in companies running the two phase 3 studies in parallel with very similar protocols and data to be captured. Issues surfacing in one of the studies usually also manifest themselves in the other study, probably to a different degree but generally trending towards the same direction.

In addition, many studies suffer from the same risks irrespective of the indication or therapeutic area. Such standard risks include delays in the reporting of SAEs, non-adherence to in- and exclusion criteria, protocol deviations in general, delays in enrollment, and delays in data entry and response to queries. Since these are very common risks for studies, one can learn in particular from the mitigation actions that worked for other studies and implement those right from the very beginning into all new studies as well as any ongoing studies.

In Figure 6, sites in a study did not respond to queries in a timely fashion e.g. within five days after a query had been posted in the EDC system. There is, however, a trend indicating that site monitoring visits had a positive effect on the non-responded queries in that the curve trended towards the green zone/design space zone after those visits. This is a pattern one can observe in many studies.

6. What KRIs worked the best and should they be accepted as corporate standards?

Depending on the indication and the potential risks identified, one could easily identify key risk indicators that work well and those that have a limited benefit.

If a KRI has a direct link to the risk, then such a KRI will—with a very high likelihood—generate an alert when the risk starts materialising. An example is the risk of many protocol deviations. The KRI is based on a metric which counts the number of protocol deviations, with a threshold of e.g. two protocol deviations per patient. With such a KRI in place, an alert would have almost 100 per cent likelihood that the risk has happened.

In a different case, the KRI may not be as specific. If the risk in a study is that patients may develop a Drug Induced Liver Injury (DILI) and the identified KRI is the number of SAEs, then the KRI may create an alert; however, this alert may be due to other SAEs patients developed and not necessarily the increased number of DILIs.

Preferably, an organisation should develop a set of "corporate" KRIs for risks that an organisation wants to keep under control. Those could be protocol deviations related to the informed consent process, timely reporting of SAEs by the site to the sponsor company's drug safety department or the number of patients lost to follow up.

In addition, one could develop therapeutic area-specific KRIs, for

Figure 5: Protocol deviations per patient across all sites in a study.

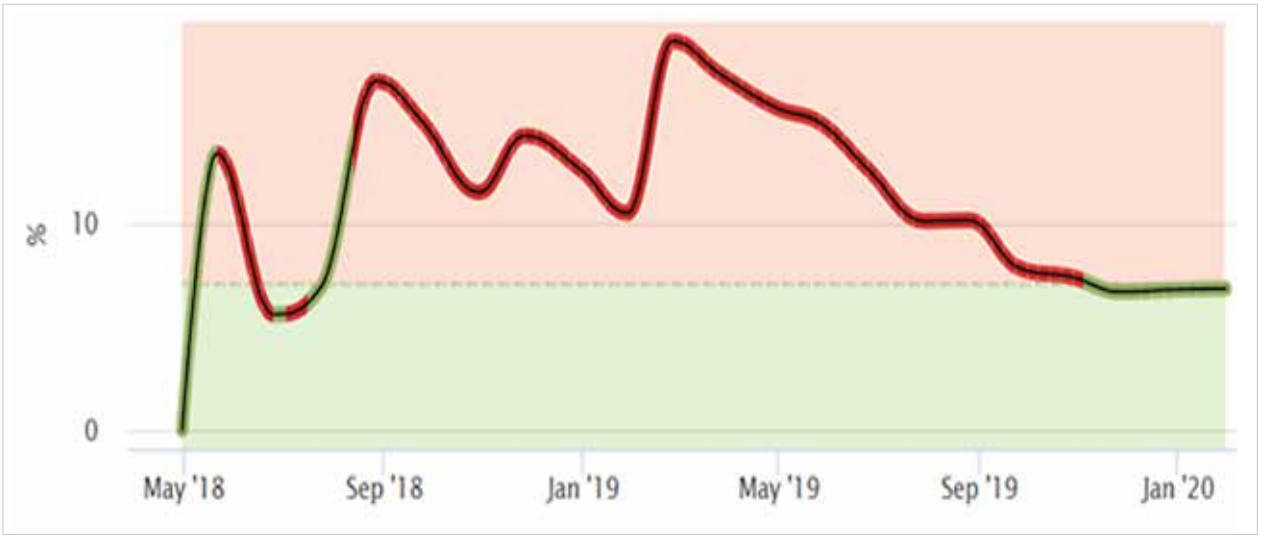

Figure 6: Per cent of overdue queries not responded to within five days after query posting in the EDC system.

risks that are related to a specific indication of interest. These KRIs could be related to the main efficacy parameter for that therapeutic area or indication (such as an acceptable number of missing endpoint/outcome data) or the acceptable number of missing lab samples for the safety profile of the drug.

Finally, a study may require a certain KRI since the study has a unique risk only applicable to this study. An example could be the balanced allocation of the patients to the strata required by the protocol, such as 50 per cent of the patients to be older than 65 years and 50 per cent of the patients to be younger than 65 years.

Benefits and return on investment

In many organisations, senior management may ask for the benefits of the implementation of a RBQM process and system, and for the return on investment (ROI). Does it make sense and what is in it for them/for the organisation if they follow the guideline? In the following section a couple of benefits and aspects of ROI will be addressed.

The first benefit is the overall better oversight of a study or a series of studies. Such oversight—whether for internally managed studies or for outsourced studies—is required by the authorities. In addition, an RBQM system provides an early warning system in case a study, a country or a site deviate from the expected performance. It also facilitates the comparison between or across CROs and thus helps in the selection process for future studies.

Secondly, an RBQM system implementation contributes to a major reduction in SDV. This SDV process – as described in the introduction – does not add significant value to the overall quality of a study. On the other hand, it is one of the costliest processes in study conduct and requires about 20 to 25 per cent of the budget. Site monitors could spend more time on truly value-adding activities at the site, such as source data review, and reduce the overall time spent at a site.

Thirdly, keeping the most important data and processes in a study under control adds to the overall availability of primary and secondary efficacy data, such as endpoint or outcome data. If missing endpoint data become an issue during the conduct of a study, one can intervene early on and thus reduce the overall rate of missing data. That, in turn, ensures more reliable statistical analyses by reducing the variance of the primary and secondary endpoints. It also contributes to a reduction of the required number of patients in a study.

Another major problem in clinical studies is the number of protocol deviations. Those deviations may originate from a complex protocol or from poor-performing or poorly trained site staff. The more (major) protocol deviations that surface in a clinical study, the less likely health authorities may accept such a study as demonstrating the efficacy and the safety of a new molecule. In addition, protocol deviations in early phase studies may have a negative impact on the interpretability of the results and thus—in the worst case—contribute to a wrong decision on whether or not to continue developing a new molecule.

Since patient safety is a major aspect of running clinical trials, a sponsor company must ensure that all safety aspects are being kept under control. Those safety aspects include timely reporting of SAEs, proper reporting of adverse events by the site staff, and the early detection of safety issues hidden in the data. The latter can easily be identified by the centralised statistical monitoring tool, facilitating a review of many numeric data without the need for a programming or statistical background.

A threat to the acceptance of study data and approval by the health authorities are inspection findings. An inspector usually focuses on the quality of the critical data and reviews also the critical processes generating those data. If there are too many major or critical findings identified, an approval of a new compound may be jeopard-

ised. The implementation of RBQM will reduce the number of inspection findings and thus increase the likelihood of the new drug approval.

Many risks in a study are more related to the overall performance of the sites and internal staff working on a study. Examples include the timely entry of data, the response to queries, the closure of properly responded-to queries, or the upload of external third-party data (e.g. central lab, bioanalytics). All of the above can have a negative impact on the final database closure date, a pre-requisite for the start of the statistical analysis. The reduction in time between the last patient last visit and the database closure has a major impact on the return on investment—assuming the drug under investigation worked.

All of the above aspects have a positive impact on the ROI when an RBQM process and system are implemented. The magnitude depends on the number of studies using RBQM, the complexity of the studies, the time saved and having clean data available earlier, the number of available endpoint/outcome data and the resources saved by not having to conduct 100 per cent SDV. It requires training on the concept and the specificities of RBQM and an underlying change management process. Once implemented, however, the benefits of an RBQM implementation are quickly demonstrated and realised.

Summary

ICH E6 (R2) (and R3) [3][7] as well as ICH E8 (R1) [8] are guidelines that have been released and are expected to be implemented by the pharmaceutical industry and CROs. The focus of these guidelines is on the quality of the data generated in clinical trials as well as patient safety and patient rights. The details are being addressed in the sections related to RBQM.

The frequently asked question, specifically by senior management, is about the true benefits and the ROI one could generate by the implementation of RBQM. The response to such a question is, that there are many benefits, such as:

- Better oversight
- Reduction of SDV
- More complete endpoint and outcome data/primary and secondary efficacy parameters
- Fewer protocol deviations
- Complete picture of the safety in the study
- Fewer inspection findings
- Overall process control
- Earlier database closure and availability of the statistical analysis

The ROI depends a lot on various study and compound parameters. Methods to calculate the ROI are available upon request to the author of this paper. |

Literature

[1] Stokman P, et al.: Risk-based Quality Management in CDM—An inquiry into the value of generalized query-based data cleaning. Journal of the Society for Clinical Data Management. 2020; 1(1): 1, pp. 1–8. DOI: doi.org/10.47912/jscdm.20 (last accessed: 15.08.2023).

[2] ICH E6 (R1) – Guideline for Good Clinical Practice. July 2002. CPMP/ICH/135/95. URL: www.ema.europa.eu/en/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf (last accessed: 15.08.2023).

[3] ICH E6 (R2) Guideline for good clinical practice Step 5. 1 December 2016. EMA/CHMP/ICH/135/1995. URL: www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf (last accessed: 15.08.2023).

[4] TransCelerate: Risk Based Monitoring Solutions. URL: www.transceleratebiopharmainc.com/assets/risk-based-monitoring-solutions/ (last accessed: 15.08.2023).

[5] Alsumidaie M et al.: RbM Guidance Document: Ten Burning Questions about Risk-Based Study Management. Applied Clinical Trials. 13 January 2015. URL: www.appliedclinicaltrialsonline.com/view/rbm-guidance-document-ten-burning-questions-about-risk-based-study-management (last accessed: 15.08.2023).

[6] Metrics Champion Consortium – Keith Dorricott: Risk Evaluation and Control – Meeting the Requirements of ICH E6 (R2). URL: https://icr-global.org/media/1476/keith-mcc-risk-workshop-icr.pdf (last accessed: 15.08.2023).

[7] ICH E6 (R3) Guideline on good clinical practice (GCP) – Step 2b. 25 May 2023. EMA/CHMP/ICH/135/1995. URL: www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-e6-r3-guideline-good-clinical-practice-gcp-step-2b_en.pdf (last accessed: 15.08.2023).

[8] ICH guideline E8 (R1) on general considerations for clinical studies. 14 October 2021. EMA/CHMP/ICH/544570/1998 URL: www.ema.europa.eu/en/ich-e8-general-considerations-clinical-studies-scientific-guideline (last accessed: 15.08.2023).

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