A risk-based quality control approach of Clinical Trials from a GCP institution in China

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Research

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Abstract

Background

This paper developed and described a risk-based quality control approach of clinical trials for clinical trial sites to improve the quality control process and ensure the quality of data.

Methods

Based on the trial experience, well versed experts and the findings of previous literature, an integrated risk-based quality control approach is developed centered on three cornerstones: risk assessment, central data review, and triggered, adaptive on-the-spot or remote inspection.

Results

We have developed an innovative risk-based quality control approach for clinical trials including risk assessment, development of quality control plan, implementation of quality control activities, development and review of quality control report, undertake actions arising from quality control report, and the update of risk assessment results or quality control plan, which fuses the idea of PDCA circle and quality by design.

Conclusion

Our RBQC methodology can significantly improve the clinical quality control process and the monitoring-audit triggered procedure can synchronize the activities of site, sponsor and CROs to achieve all-win. It is an innovative and effective approach.

Background

Clinical trials require measures such as site quality control and CRA monitoring to ensure the compliance with GCP, to assure data integrity and reliability of study results, and to protect subjects’ rights and safety. Since ICH (International Conference of Harmonization) GCP recommends international implementation of innovative approaches to quality risk management in addendum to ICH E6 in 2016[1], RBM (risk-based monitoring) has got a lot of attention in recent years. Many sponsors and CROs have developed various approaches on RBM[2,3,4]. The data showed that RBM can significantly improve the clinical oversight process and shows distinct benefits in quality, timelines, and cost[5, 6, 7, 8, 9]. But effective RBM also needs a similar quality control process for clinical studies at study sites. Therefore, as a clinical trial site in china who is a member of ICH, based on the regulations, our trial experience and well versed experts, we developed an innovative risk-based quality control approach to keep pace with international regulations and the RBM approach of sponsor and CRO.

Materials And Methods

Our GCP institution, based at Cangzhou central hospital, was established in 2013 and gained much experience in managing and implementing clinical trials. We have registered 29 clinical majors in NMPA and conducted over 200 clinical trials including cardiovascular, endocrinology, oncology, hematology, neurology, nephrology, infection, and dental trials involving investigational medicinal products, devices, and diagnostic reagents. Our team members well versed with the regulatory guidelines, experienced in
clinical research and drug safety, and professional in the design, development, delivery, data management and statistical analysis of clinical trials. Based on these, we have developed a risk-based quality control approach to ensure the conduct and delivery of clinical trial with high quality, centered on three cornerstones: risk assessment, central data review, and triggered, adaptive on-the-spot or remote inspection.

**Results**

Process

The steps of our risk-based quality control approach for clinical trials include: risk assessment, development of quality control plan, implementation of quality control activities, development and review of quality control report, undertake actions arising from quality control report, and the update of risk assessment results or quality control plan, as shown in Fig. 1.

Responsibility

We set four oversight groups for the risk-based quality control approach: the Trial Management Group (TMG), the Quality Control Team (QCT), the Independent Data and Safety reviewing Committee (IDSRC) and the Senior Quality Management Committee (SQMC).

TMG is concerned with day to day running of the trial to real-time control the trial quality. QCT is composed by full-time QC technicians, clinical professionals and good CRCs, cooperating with TMG to conduct the triggered, adaptive on-the-spot and remote inspection. IDSRC provides an independent body reviewing study data blindly to ensure data are always considered and compared in the same way. IDCRC is responsible for central data review, including statistician and medical staff at least. SQMC, which consists of our institution Director, Head of GCP office, Quality Assurance Manager of GCP office, Data Manager of GCP office, Head of clinical trial majors, Head of medical statistics, Head of Information Systems, is charged for risk assessment, critical data definition, quality plan review and determination for each trial before implementation, and considering the recommendations of the IDCRC and making the ultimate decision for trials.

Risk assessment

The work involved in risk assessment are briefly summarized as: protocol review, initial trial risk assessment, critical definition, and risk-based quality control (RBQC) plan development.

Through protocol and literature review, SQMC undertakes the initial trial risk assessment to assess some risk points such as safety of the investigated product (IP), complexity of the trial, and the operational experience of research team, and defines the critical data and process to develop an initial RBQC plan.

In this step, the potential risks and critical data are identified and a set of risk indicators are selected. The identified potential risks are further categorized and given a score on the basis of their impact on the data
quality. The risks are classified into 3 categories (3-severe; 2-moderate; 1-mild) according to the magnitude of the impact on the study result. Mild risks can be easily revised, usually having a little or no impact on the conduct and result of the study. Moderate risks also can be revised, but may cause the trial quality decline and some serious outcome if incorrectly implemented, such as degradation of performance, disruption of schedule and increased cost. Severe risks cannot be rectified if overlooked, severely affecting the trial and may cause failure of the trial, such as critical data missing, insufficient sample size and other severe performance problems. After classification, each risk is given a score on the basis of the trial details. The score of mild risks is on a scale of 1–3; moderate risks are given a score from 4–6; score range of severe risks is 7–9; the higher the score, the higher the risk. The score of each risk varies with different trials, but the category of risks is relatively faxed. Table 1 shows the major risk points and their category.
Table 1
Major risks and the category

| Risks                                                                 | Category |
|-----------------------------------------------------------------------|----------|
| IP safety                                                             | mild     |
| complexity of the trial design                                        | mild     |
| operational experience of research team                               | moderate |
| Inadequacy of documents                                               | mild     |
| Inadequacy of IP caused by shipment delay or failure to maintain cold chain | mild     |
| Unreasonable delegation of responsibilities to investigators          | mild     |
| Incorrect data clarification                                          | severe   |
| Delay in data clarification                                           | moderate |
| Poor subject availability                                             | mild     |
| Too-slow or too-fast recruitment                                      | moderate |
| High screen failure rate                                              | mild     |
| High protocol violation rate                                          | moderate |
| Change in investigators                                               | moderate |
| Incomplete documentation                                              | moderate |
| IP loss                                                               | severe   |
| Incorrect IP assignment                                               | severe   |
| Inappropriate IP accountability                                       | moderate |
| Primary data missing                                                  | severe   |
| Inappropriate management of AE/SAE                                    | moderate |
| Noncompliance with SAE reporting requirements                          | mild     |
| Missing SAE report                                                    | severe   |

The risk scores are then summarized to obtain an overall trial risk score, which, along with the individual risk scores, form the basis of a recommendation on how to implement QC intervention for each trial, and then the QC plan, which is a document describing all QC activities for a particular trial, details of planned central data review and on-the-spot or remote inspection, and relevant timelines, is developed. When the
percentage of overall trial risk score account for the total score is higher than 60%, the trial is classified as high-risk trial; similarly, when the percentage of overall trial risk score is greater than 30%, the trial is a moderate-risk trial, otherwise it is a low-risk trial. High-risk trials are marked as prioritize and are processed firstly, followed by moderate-risk trials marked as increase, may needing increased intervention. Low-risk trials are marked as maintain or decrease, can be optionally reviewed but do not require more intervention.

As a result of risk assessment, the data that are essential to the reliability of data and that support the primary objectives of the trial, such as primary endpoints, patient safety data on adverse events, and reason for withdrawal during the treatment period, are adopted as critical data. The consent process, recruitment and retention, randomization, specific, predefined study visits, IP handling process and other important process affecting heavily on the quality of data are selected as critical process.

The risk points with score higher than 6 and the critical data are selected as risk indicators. In addition, the threshold for toleration of these indicators for detecting risks at each risk indicator are determined and ranked in decreasing order—3(trigger remote inspection), 2(trigger on-the-spot inspection by source data verification), and 1(trigger on-the-spot inspection by source data review and source data verification).

Quality control activities

There are essentially two kinds of quality control activities: central data review and triggered on-the-spot or remote inspection.

Central review

Central review is centered on reviewing the accumulating data of a trial using analytics to explore unusual patterns in data, detect inconsistencies in data, predict potential issues and risks, and correct problems in the execution of a clinical trial. It includes 4 parallel kinds of review: risk review, medical review, statistical review, and data review. The risk review is centered on detecting individual risk indicators and overall trial risk based on the results of risk assessment to make recommendations to adjust QC intervention. The medical review is performed by medically trained staff to review and inspect patient data holistically to assess subject safety, protocol deviations, and other clinical issues that may degrade data integrity and trial quality. The statistical review allows statisticians to explore data bias, fraud, process failing, and other quality issues. The data review is aim to detect and manage erroneous, missing and inconsistent data.

The latest data from electronic data capture system (EDC), electronic case report form (eCRF), the Interactive Web Response System (IWRS) and other sources are used for central review. Central review is a typically monthly activity involving periodic assessment.

After Central review, the review results are reviewed at a monthly risk evaluation meeting to facilitate an appropriate adjust on the trial level (3 to 1) for each trial.
Adaptive and triggered on-the-spot or remote inspection

Excepting the routine on-the-spot or remote inspection in accordance with the QC plan, there are still four ways to trigger on-the-spot inspection: TMG, central review and sponsor audit or CRA monitoring. When the TMG or central review finds the risk indicators over the threshold, on-the-spot or remote inspection would be triggered according to the mean grade of the indicators. When the mean grade is 3, remote inspection on the data from electronic data capture systems, eCRF, IWRS, and laboratory report in our office and inquiries to sites by phone or email are triggered; when the mean grade is 2 and 1, on-the-spot inspection by source data verification for critical data and on-the-spot inspection by both source data review and source data verification for critical data are triggered respectively. QCT performs on-the-spot inspection by source data review immediately while receiving the subscription of sponsor audit or CRA monitoring and it should be completed before the implement of data audit or monitoring.

Discussion And Conclusion

The risk-based quality control approach described in this paper is established and adopted by our institution in March 2019, which is aim to promote the efficiency of quality control activities and contribute to the data reliability. Compared with traditional quality control approaches such as regular quality control activities and 100% SDV, we have found that the RBQC is more adaptive and more beneficial in data quality, consistent with the findings of reported studies\textsuperscript{[6,10]}. From March 2019 to now, we have observed that RBQC resulted in 33.6% fewer significant issues per site monitoring, 41.5% fewer significant issues per sponsor audit, 25.6% higher mean interval between quality control activities, and 20.1% lower mean time cost per on-the-spot inspection in 9 clinical trials. We also found that the frequency of on-the-spot inspection and the risk level of 8 trials showed a decreasing tendency over time.

These results significantly indicate that our RBQC methodology can significantly improve the clinical quality control process and the monitoring-audit triggered procedure can synchronize the activities of site, sponsor and CROs to achieve all-win. It is an innovative and effective approach.

However, we still need to develop an intelligent and automate deployment and technology solution of QC comprising the risk assessment and categorization tool based on a template designed by TransCelerate\textsuperscript{[11]}, a clinical data repository that supports real-time data acquisition, mapping, and integration of clinical trial data from clinical trial management systems, e-CRF, EDC, IWRS, HIS and other electronic data provided by central laboratory or imaging vendors, and data alert module.

Declarations

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Availability of data and materials
The data or materials used and/or analyzed for the study will be available from the corresponding author on reasonable request.

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Authors’ contributions

LWH and WYR conceptualized the invention and contributed to the design of RBQC, performed some of the analyses, drafted the initial manuscript, and approved the final manuscript as submitted. CR conceptualized the invention and led the design and development of the RBQC and contributed to the manuscript. DXY conducted the implementation of the RBQC processes and contributed to the manuscript.

Ethics declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures
Figure 1

The process of our risk-based quality control approach