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Construction and Application of a Clinical Trial Quality Risk Control System Based on the Six Sigma DMAIC Model

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Abstract: According to the DMAIC method of Six Sigma, a quality risk control system for clinical trials at the large hospital should be built, and the main risk areas and governance paths need to be determined. According to the back-end data from a third-tier Grade A hospital in 2021–2025, both industry-sponsored trials (ISTs) and investigator-initiated trials (IITs) were chosen. A total of 937 problems has been identified so far, and among them, 715 will be the subjects of this study from 2023 to 2025. The 11 risk areas have been partitioned, and according to the Pareto analysis method, frequency-based sigma (σ) priority indicators and the DMAIC process model will be used for evaluation. The first seven kinds of risk were about 89.9 per cent. The first were source data and documentation (182 items, 25.5%, σ = 2.16), and next was informed consent and participant rights (102 items, 14.3%, σ = 2.57). IIT projects had a relatively high number of problems per project compared with IST projects in general; in 2024, it was 11.80 problems per project and dropped to 6.50 in 2025. During the pre-startup quality control, there were 52 defects, and about 98.1 per cent of them have been rectified. In short, there are two types of risks in clinical trials, and among them, "vital few" refers to a small number of aggregation points in some areas. Embedding DMAIC in all links of the clinical trial process and combining it with corrective and preventive actions (CAPA) and risk-based process management will build a quality risk control system based on a structured issue database, key risk indicator (KRI) early warning mechanism, proactive prevention and closed-loop rectification.

Keywords: Six sigma; DMAIC; Clinical trial; Risk management; Quality control; On-site inspection

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1. Introduction

Clinical trials are a necessary step in the development process of drugs, medical devices and other therapies that takes them from the laboratory to practice. Recently, the joint development of innovative drug and device research, real-world studies, investigator-initiated trials (IITs) and multicenter collaborative research has expanded the scope of hospital-based clinical trials beyond standardized registered studies, and these

complex research scenarios have many different protocols and various types of data. With the expansion of the scale and complexity of the project, more problems are likely to occur in all links of the operation; thus, the old model that is only based on experience and addresses problems after they arise is no longer suitable for high-quality development.

The first reason for the quality management of clinical trials is to protect the rights, safety and interests of the subjects of the trial, and at the same time ensure the reliability and completeness of the data from clinical trials. In accordance with the 2020 Good Clinical Practice (GCP) guidelines in China and the 2022 Good Clinical Practice for Medical Device Clinical Trials, full-process quality management should also be carried out. In accordance with ICH E6(R3) and the risk-based monitoring guidance of the FDA, the monitoring resources should be employed to protect the subjects and guarantee the quality of the data [1–5]. The management of the enterprise has started to control at all links and well in advance of any problems; it seems that a proactive and risk-averse attitude has begun to form in the company's operations.

Previous studies have made many valuable contributions to the identification of risks, assessment tools and indicator systems at all stages of clinical trials, some of which have integrated PDCA or Six Sigma concepts [6,7]. Most are still in the form of qualitative summaries and do not offer specific ways to prioritize problems, catch them at the source, and address them continuously. The five stages of the DMAIC model in Six Sigma are: Define, Measure, Analyze, Improve and Control; it is a closed-loop system that has been used to solve problems in infection control and improve the overall safety of hospitals [8]. Based on the on-site inspection data from the IST and IIT projects of a tertiary Grade-A hospital in 2021–2025, this paper will present the inspection results and build an iteratively sustainable DMAIC-based quality risk control system.

2. Materials and methods

2.1. Data sources

Collect the on-site inspection data of a tertiary Grade-A hospital during the clinical trials of the IST and IIT projects from 2021 to 2025 retrospectively, and then analyze this data in this paper. The scope of the inspection included informed consent, protocol execution, protection of participant rights, study documentation, operational quality control, pre-startup quality control, etc. A total of 937 identifiable issue records were obtained, and among them, the 715 from 2023 to 2025 served as the subject of risk domain consolidation, σ based priority ranking and DMAIC control rule design. All the data was anonymized before analysis.

2.2. Data processing and inclusion criteria

Data consolidation should be carried out in line with the rule of "preserving the original semantics of the issue, standardizing statistical criteria, and avoiding duplicate inflation" and "issue category count" is the number of categories in the data, and "issue frequency" is how often the same type of issue occurs; these two indicators are shown separately. A quality control ledger entry will only be added to the statistics if there is a clear quality control checkpoint and rectification information. All the items were given the same risk group in the combined analysis based on their original data source ID.

2.3. Risk domain classification

According to the demands of GCP and the structure of the quality control form for hospitals, all the original problems have been organized into eleven risk domains: informed consent and participant rights, source data

and documentation, trial documentation and archiving management, personnel qualification/authorization and training, protocol execution and deviation management, investigational product/device management, safety event reporting, regulatory compliance document management, biological sample management, facilities/equipment and supplies management, and other management issues. The three focuses of the CFDA data verification have been covered, and it is in line with the important quality attributes in ICH E6(R3) [9].

2.4. Six sigma measurement frameworks

Historical quality control ledgers did not systematically record the total number of inspection opportunities (that is to say, the denominator) for each risk indicator, and thus the manufacturing-derived DPMO metric could not be directly used. The proportion (p) of the frequency of an issue in a particular risk area relative to the total frequency is used to calculate a standardized risk priority index as via $\sigma = \Phi^{-1}(1 - p) + 1.5$; this value is for relative ranking of data from the same source and does not need to be employed in an absolute process capability comparison of different institutions.

2.5. Statistical analysis

Descriptive statistics were used to show the distribution and proportion of the problems. To find the causes of this, Pareto analysis was employed; then, σ values were used to rank the severity of risk at all levels, and according to them, a risk governance model in line with the DMAIC process was constructed. Excel and Python were used to analyze the data, and all the charts were drawn by hand.

3. Results

3.1. Introduction to the survey results

From 2023 to 2025, the hospital has been conducting regular on-site audits of all the clinical trials it is carrying out; by consolidation, a total of 715 problems has been identified in the 39 ongoing projects (23 IST and 16 IIT).

The number of problems per IIT project was relatively high compared with that of an IST project. The two were relatively close in 2023; that is to say, IST was 4.20 issues/project and IIT was 4.60 issues/project. According to the IIT forecast in 2024, the number of problems per project will reach 11.80 and exceed the concurrent IST rate of 3.00 significantly; the main reasons for these problems are the failure to complete the CRF, inconsistency between source documents and the database, and delayed update of investigator authorization records. By 2025, the IIT issue will be 6.50 per project; however, it will still be higher than the IST rate of 5.25 per project (**Table 1**). IIT projects do not have regular supervision and support from the sponsors and contract research organizations (CROs), and the investigators are required to be responsible for both the clinical care of patients and research activities at the same time; thus, there is a higher probability of defects in the upstream process. Thus, these projects are not easy, low-risk research on the first sight.

Table 1. Categories of projects and issue statistics from on-site inspections, 2023–2025

Year	Project type	Projects inspected	Issue categories	Issue frequency	Frequency /Project	Remarks
2023	Active IST	10	18	42	4.20	
2023	Active IIT	5	16	23	4.60	
2024	Active IST	5	7	15	3.00	

2024	Active IIT	5	32	59	11.80	Concentrated surge
2025	Active IST	8	29	42	5.25	
2025	Active IIT	6	23	39	6.50	
Total	—	39	125	220	5.64	

3.2. Distribution and pareto analysis of the consolidated risk domain

After the consolidation of unified risk domains (n = 715), source data and documentation ranked first with 182 issues (25.5%, σ = 2.16); therefore, it can be concluded that the problem of inconsistency between source data and CRFs is still very serious. Informed consent and participant rights made up for 102 problems (14.3%, σ = 2.57), and they mainly took the form of non-standardized signing time points, version inconsistencies, etc. The sum of the top seven risk areas was 89.9%, as shown in **Table 2**. Trial documentation and archiving management (94 cases), personnel qualification/authorization and training (80 cases), investigational product/device management (69 cases), facilities/equipment and supplies management (58 cases) and protocol execution and deviation management (58 cases) made up the second tier.

Table 2. Distribution of risk domains, σ values and management priority from on-site inspections, 2023–2025 (n = 715)

Risk domain	Freq.	Proportion (%)	Cumul. (%)	σ value	Management level	Primary control direction
Source data and documentation	182	25.5	25.5	2.16	Level I Targeted improvement	First-case data audit, source data/CRF consistency check, logic validation
Informed consent and participant rights	102	14.3	39.7	2.57	Level I Targeted improvement	ICF version tracking, signing process checklist, compensation clause verification
Trial documentation and archiving management	94	13.1	52.9	2.62	Level II Key monitoring	ISF catalog standardization, approval filing deadlines, electronic ledger alerts
Personnel qualification/ authorization and training	80	11.2	64.1	2.72	Level II Key monitoring	Authorization/role dynamic updates, certificate alerts, role segregation
Investigational product/ device management	69	9.7	73.7	2.80	Level II Key monitoring	Receipt/dispensing/return/destruction closed-loop, temperature and humidity control
Facilities, equipment, and supplies management	58	8.1	81.8	2.90	Level II Key monitoring	Calibration certificate alerts, storage environment audits, shelf-life management
Protocol execution and deviation management	58	8.1	89.9	2.90	Level II Key monitoring	Visit window alerts, deviation reporting deadlines, IIT pre-startup review
Regulatory compliance document management	23	3.2	93.1	3.35	Level III Ongoing control	Approval expiry dates, recruitment materials, HGR/filing document management
Biological sample management	22	3.1	96.2	3.37	Level III Ongoing control	Collection/processing/transport/retention record consistency audit
Safety event reporting	17	2.4	98.6	3.48	Level III Red-line management	AE/SAE identification, 24-hour reporting and follow-up closed-loop
Other management issues	10	1.4	100.0	3.70	Level III Ongoing control	Include in issue database for review; identify institutional blind spots

σ is a normalized priority index that shows the proportion of risks based on their frequency; it is only for the relative ranking of items in the same data set.

3.3. Upstream interception effect of pre-start quality control

By 2025, the new pre-startup quality control initiative had found 52 problems in the protocols, informed consent forms, insurance, agreements, approval documents, standard operating procedures (SOPs), emergency plans, storage facilities and instrument calibration certificates. Of these, 51 were corrected, and the rectification rate was 98.1%. To reduce the risk of non-compliance due to version errors or missing documents before the start of work, it is recommended that quality control be carried out earlier in the timeline, during the pre-startup stage; thus, later rectification costs will be reduced and the quality management concept of "prevention is better than cure" will be realized.

3.4. DMAIC control rules

According to the analysis above, control rules based on DMAIC have been set up (**Table 3**). At the management level of IST and IIT, determine the attributes required for the CTQ items related to the protection of participants and data security. A measure stage is employed to construct a single problem database, and the problems are organized into three tiers according to the "main risk domain", "secondary issue type" and "tertiary issue description". Pareto and root-cause analysis will be employed here to find the underlying reasons for the risks in this section. The improvement period will carry out the three forward shifts: pre-project review, pre-first-case training and post-first-case data audit. In the control period, the KRI dashboard will still monitor the closed-loop rectification rate and the recurrence rate; although the frequency of these indicators will be low, they are highly significant and will be listed as red-line management items.

Table 3. DMAIC-based clinical trial quality risk control rules

DMAIC phase	Findings from this study	Key indicators/Tools	Improvement and control rules
D (Define)	Risks concentrated along two main themes: participant rights and data quality; IIT risk exceeds IST	CTQ, project risk classification, KRI catalog	Set stratified management objectives by IST and IIT; add pre-startup review for IIT protocols, CRF, and statistical support; contract review to assess compliance and rationality
M (Measure)	Historical ledgers exhibit multiple coexisting statistical criteria	Unified issue database, frequency, project issue rate, σ priority	Establish three-tier issue classification to prevent duplicative inflation of the same issue; data entry should be completed within 7 calendar days
A (Analyze)	Top 7 risk domains cumulatively account for 89.9%; source data/documentation and informed consent are dual high-frequency risks	Pareto chart, fishbone diagram, recurrent issue tracking	Conduct root cause reviews for informed consent, CRF/source document, and IIT composite issues; evaluate impact of protocol deviations on result reliability
I (Improve)	Pre-startup QC identified 52 issues; 51 rectified	Pre-startup checklist, ICF process checklist, first-case data audit, CAPA system	Implement three forward shifts; establish CAPA closed-loop (identification → documentation → assessment → investigation → action plan → execution → closure)
C (Control)	Low-frequency issues (SAE, expired approvals, drug/device temperature control) carry severe consequences	KRI dashboard, closed-loop rectification rate, recurrence rate	Monthly or quarterly monitoring; recurrent issues trigger SOP revision, system alerts, or targeted training; red-line indicators are monitored continuously regardless of frequency

4. Discussion

4.1. From “issue frequency” to “risk priority”: The applicability boundary of six sigma in ledger-based data

Generally, quality management ledgers for clinical trials only list the problems that have been found and do not track the total number of inspection opportunities. To use the DPMO index of manufacturing and the other statistics arbitrarily is likely to be statistically overfitted. Based on the frequency composition of risks in this study, we have derived sigma values for relative ranking to help managers know which types of risks are concentrated in the data source and should be dealt with first. In this way, they will be more comparable and not mix up the count of inspection records, the count of issue categories, and the frequency of issues.

4.2. The enduring problem of informed consent and process-oriented control

Generally speaking, the proportion of problems in informed consent was 14.3% (102 cases), and it was one of the main compliance red-line risks. There were problems with the lack of a specific signing time, missing signatures or dates, version inconsistency, and insufficient explanation of the compensation clause. Informed consent should be considered a document, but it does not have the foundation of a process. We propose to divide the process of obtaining informed consent into five stages: disclosure of information, confirmation of understanding, exercise of free will, signing and saving of the version, and then construct an ICF process audit checklist based on these stages. Projects in the IIT should specify more clearly the compensation, insurance, damage liability and privacy protection of people to avoid compliance risks due to the vagueness of the template.

4.3. Source data and documentation are the core of operational quality control

The source data and documentation were mentioned in 182 cases (25.5%) the most frequently. A reliable basis for the results of the trial is the logical consistency of the source data, CRFs and databases; the design of the CRF and standardization of data collection directly affect statistical analysis and the interpretation of results [10]. Other typical reasons are that the lab test results were submitted late, there was no signature and date on the CRF correction, or it was done off-site without a deviation report. At the beginning of the registration for first-time and early-enrolled patients, hospitals should carry out source data/CRF consistency audits, and intervention tools such as audit checklists, logic checks in the electronic data capture (EDC) system and scenario-based training can be employed. Data entry should be completed within seven calendar days after the creation of the data.

4.4. Different quality support for IIT projects

According to the data from the on-site inspection, the proportion of problems per project in IIT projects was higher than in IST projects and was relatively concentrated in 2024. Based on this pattern, sponsors and CROs are not regularly supervised in the above studies; thus, there is a higher risk that investigators may have had defects in the up-stream stage of protocol design, CRF design, data management, document archiving, etc [11]. Establish a pre-start quality control system for the IIT project in the hospital, carry out an initial feasibility assessment of the protocol, check for CRF compatibility, and jointly plan how to manage and analyze the data. If they have the funds, the hospitals will set up a support station. Projects organized by IIT in cooperation with foreign institutions should also be covered by the regulations on the approval of human genetic resources.

4.5. Do not ignore low-frequency, high-consequence risks because they are ranked low in frequency

The number of times safety accident reports were filed (17 times), the management of regulatory compliance documents (23 times), and the handling of biological samples (22 times) were relatively small; however, had any of them happened, it would have been a very serious problem. The six-sigma model will be based on the main quality indicators and not only on how many times they occur [12]. The KRI framework should have a delay in the reporting of serious adverse events (SAEs), and the disposition rate of drug/device temperature control anomalies and the non-renewal rate of expired approvals are to be included in the red-line indicators and regularly monitored, irrespective of how frequently they occur. Projects that are for the export of human genetic resources should have a special person in charge of handling regulatory filings before the start of the project.

4.6. Implementation paths

Based on the above analysis, hospitals can carry out the five stages of DMAIC. First, establish a cooperative governance system comprising an institutional review office, clinical department, project team, quality control officer, etc., clarify the responsibilities of each link, and carry out regular on-site quality supervision of high-risk projects. Second, establish a complete life-cycle risk control process to carry out risk identification at all times, from the start of the project, construction, operation, site handover, archiving, etc. Thirdly, organization and digitization of the quality control ledger will be carried out; with the help of an advanced information system, hospitals can add quality control checkpoints to the CTMS to automate the tracking of closed-loop rectification. Fourthly, in terms of the training form of situation-based teaching, we will present de-identified historical problems in the form of real cases. Fifth, build an incentive and punishment system to address the long-standing problems and reward the low-risk team that has maintained a good record. The institutions and sponsors should work together to release information and adjust the management measures accordingly.

4.7. Limitations

As it is a single-center, retrospective quality management study, the results may not be the same in other circumstances. Some of the original problem descriptions are not detailed enough, and even after classification, there may still be subjective judgment bias. Historical ledgers did not have the full opportunity-count denominator, so the σ values can only be used as a risk priority reference in the same data source and are not strict process capability assessments. The 2025 data were subject to changes in the ledger version and had an incomplete statistical cycle, so they could not be directly compared with the full calendar year. In light of the future structure of this issue database, multicenter research will be carried out; the opportunity-count denominator for each type of risk will be recorded, and KRI dynamic early-warning systems and pre-post intervention-controlled designs can be added to further assess the actual improvement effect of the DMAIC mechanism.

5. Conclusion

According to the primary concentration results of the consolidated empirical analysis of on-site inspection data from 2021 to 2025, the main areas of quality risk in clinical trials are the source data and documentation, informed consent and participant rights, trial documentation and archiving management, and personnel

qualification/authorization and training at the tertiary Grade-A hospital. The two main risks of the source data and informed consent were mentioned, and together with the other six, they accounted for 89.9 per cent. Although the number of problems in the IIT project was relatively high compared with that of the IST project, they were corrected during the pre-start stage of quality control and reached a correction rate of 98.1%; thus, a "risk-forward" strategy can be used.

The DMAIC model of Six Sigma will be employed at all stages of the clinical trial, and in cooperation with corrective and preventive actions (CAPA) and risk-based process management, a risk management system for critical quality attributes will be established [13]. An organized issue database will be built, KRIs (key risk indicators) early warning mechanisms will be introduced, and proactive prevention and closed-loop rectification will be constantly carried out. Hospitals should stop using the old way of risk assessment for clinical trials in the aftermath and take proactive prevention measures; with the help of the five paths of organizational synergy, process reengineering, digitalized ledgers, capability construction and closed-loop control, data should be used for governance rather than intuition.

6. Data statement

Only the de-identified quality management ledgers of clinical trials and summary data from on-site inspections will be employed as the secondary statistics and quality improvement basis in this paper. No personal information of the participants, investigators, departments, sponsors or particular projects will be disclosed.

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