药物临床试验中心化监查统计指导原则

（试行）

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1. Introduction

In order to ensure the rights and safety of clinical trial subjects, clinical trial data

To ensure the quality and completeness of the data, the sponsor needs to monitor all stages of the clinical trial.

check. ICH E8(R1) states that the key points of the study should be identified during the study planning

quality factors and risk management of these factors during study conduct.

The increase in data volume and complexity of clinical trials has brought challenges to clinical trial monitoring.

A bigger challenge. ICH E6 (R2) and "Drug Clinical Trial Quality Management Regulations"

"Specifications" clearly states that sponsors should adopt a systematic and risk-based approach to

Clinical trials are monitored, and different monitoring strategies may be considered under different circumstances.

strategy, and emphasized the advantages of centralized monitoring. Popularity of electronic data collection systems

The widespread use and introduction of statistical evaluation methods have paved the way for the implementation of centralized monitoring

Provides conditions that, when combined with traditional on-site monitoring, can improve the quality of clinical trials

Quality and efficiency.

On-site monitoring refers to the conduct of clinical trials by the sponsor or

Its representatives conduct on-site assessments of trial quality at study centers. On-site monitoring capabilities

Ability to detect data entry errors by comparing original records with case report forms

and missing data to ensure the authenticity and integrity of research documents; evaluate the research center

personnel's familiarity with the research protocol and related processes; assess the understanding of the protocol

Compliance and completion of study drug inventory, etc. Some of the above supervisory activities or

All can also be conducted at locations other than clinical trial institutions through information technology.

Completed, its essence also belongs to on-site supervision.

Centralized monitoring refers to the use by the sponsor or its representatives of accumulated data and Remote assessment of test quality at any time and place. Centralized inspection as on-site inspection can also help adjust the frequency of on-site inspections and assist in identifying potential problems. problem data, thereby prompting the focus of on-site inspections.

At present, the main methods for clinical trial monitoring in pharmaceutical and biotechnology companies are still The old method is to visit clinical trial sites regularly and frequently. At the same time, domestic and foreign A series of clinical trials on centralized monitoring have proved the practice of centralized monitoring Methods can speed up the quality review process and enable higher quality verification of clinical trials effect. Through centralized monitoring and verification data, sponsors can monitor earlier clinical operation quality issues and carry out targeted and rapid rectification, especially those involving and multi-center clinical trials with larger sample sizes.

At present, the domestic understanding, technical research and application of centralized supervision are still at a low level. in the early stages. Therefore, it is necessary to clarify risk-based monitoring strategies and formulate relevant Appropriate implementation guidelines are essential. This guideline mainly focuses on centralized monitoring Statistical issues in , focusing on the scope and use of centralized monitoring factors that need to be considered when conducting audits, as well as the systematic risk management measures that may be adopted during audits. Accounting methods to help sponsors practice and apply centralized monitoring in method selection and provide technical guidance on implementation. These guidelines represent current views only and understanding, and will be revised and improved as research and understanding deepen.

2. Clinical trial risk management system

Sponsors should establish risk management throughout the operation of clinical trials system to ensure the reliability of clinical trial data and improve the efficiency of the entire clinical trial.

Quality management to protect the rights and safety of subjects. clinical trial risk management

The establishment of the management system mainly focuses on the following links:

(1) Key data and key processes

ICH E8(R1) states that sponsors should prospectively determine the

Critical to Quality Factors, where key data

and critical processes are important components of critical quality factors. In clinical trials

There is a difference in the importance of data and processes, and the occurrence of non-critical data and processes

Errors generally do not have much impact on conclusions about a drug's safety and effectiveness.

Errors in key data and processes will harm the rights and interests of subjects or the results of research.

reliability and completeness of the results.

Key data and key processes usually refer to (including but not limited to):

• Whether informed consent was properly obtained;

• Implementation of program admission criteria during recruitment, especially the guaranteed

Standards for examinee rights;

• Study the process system for medication recording and management;

• Safety related to clinical trial efficacy endpoints or protocol-specific requirements

Relevant to sexual endpoints (e.g., serious adverse events, death, dropout, etc.)

evaluation process system;

• Process systems related to the reliability and integrity of clinical trials (e.g.

For example, plan violation management, blind maintenance management, etc.).

(2) Risk assessment

Risk assessment usually involves identifying risks, analyzing risks, and preparing

Provide basis for risk control. Early identification of key data and key processes, their core

The focus is to implement risk assessment and management in clinical trials.

After identifying key data and key processes, the sponsor should conduct a risk assessment

assessment to identify issues that may impact the collection of critical data or the actual implementation of critical processes

The nature, sources and potential causes of risks, thereby forming risk indicators in monitoring.

Risk assessment should first identify important risks and establish the priority of risks.

Then analyze the risks, including quantitative estimates of risks and risk scope.

Qualitative description of the perimeter. During risk assessment, focus on preventing or reducing risk

Key data and key processes in clinical implementation, data collection and final reporting

Possible critical errors. Risk identification for monitoring purposes should generally consider

The types of data collected, the specific means required to collect these data, and the

Issues related to protecting the rights and interests of subjects inherent in bedside surveillance.

Risk assessment should consider the following three aspects: the likelihood of the risk occurring;

The limit to which the risk can be detected; the impact of the risk on the protection of the rights and interests of subjects and

influence on the reliability of test results. Sponsors should make decisions based on risk assessment results

Establish an audit plan (e.g., decide which risks can be addressed through auditing)

decisions) and determine the type and intensity of monitoring activities best suited to address these risks.

Sponsors can also determine which risks can be addressed through means other than monitoring

Better management (e.g., modifying programs to eliminate sources of risk). Sponsor

It is necessary to regularly assess new risks and decide whether the monitoring method needs to be adjusted.

for more effective risk management.

(3) Risk control

The sponsor should decide which risks need to be reduced and which risks are acceptable.

The methods used to reduce risk to an acceptable level should be commensurate with the significance of the risk.

symbol. Risk reduction measures can be incorporated into program design, implementation planning, and monitoring plans.

planning; roles and responsibilities should be defined among all collaborators to ensure compliance with standard practices

operating procedures and ensure training on corresponding measures and processes. risk control

Taking into account the medical and statistical characteristics of the variables and the statistical design of the trial, the

First set the quality risk tolerance (Quality Tolerance Limit, QTL),

To identify factors that may affect the safety of clinical trial subjects or the reliability of trial results

systemic problems. QTL reflects the acceptable risk indicators at the trial level

The degree of variation in execution deviation can be defined through statistical methods. in prison

Risk assessment should be triggered when it is detected that the risk indicator value exceeds the preset QTL.

To determine whether risk control measures need to be taken. The QTL should be

Setting it as early as possible will help to correct or improve the process in a timely manner to ensure clinical trials.

the implementation of experiments; the second is the management of crucial parameters that help guide and research goals.

monitoring and help design more risk-based monitoring strategies.

When setting the variation range or QTL risk indicators, the following factors can be considered:

Points (including but not limited to):

1. Experimental research data

Based on the identification of key data and corresponding risk assessment, attention should be focused on

In those situations where the value of important risk indicators exceeds the QTL. Now more and more

Most of the data comes directly from electronic source data. After presetting the QTL range, the actual

Timely measurement, tracking, reporting of current data and taking corresponding measures when necessary will much easier.

2. Test plan process

An effective mechanism should be established to promptly detect protocol violations or drug clinical violations. GMP status and assess their impact on study objectives and subjects impact on test takers' rights. Set risk indicators and QTL to monitor key issues in a timely manner key issues and trigger necessary monitoring escalations (e.g., additional on-site visits, additional program training, etc.).

3. Test management process

Risks that can be monitored centrally should be defined in the clinical trial management process. Risk indicators are used to set monitoring activities and trigger mechanisms in a targeted manner. Situations that may trigger monitoring upgrades include data entry into the eCRF system. delay, or delay in reporting serious adverse events, etc. The lack of variability in the data also Will trigger further monitoring, such as certain aspects of blood pressure measurement in antihypertensive drug trials Preference for a specific one-digit number.

Information technology can be used to integrate test data from various sources to develop A visual centralized monitoring system to monitor the test process and data quality, and compile regular audit indicator reports to record and demonstrate ongoing audit activities.

Whether the actions are carried out according to the predetermined monitoring strategies and procedures to improve the quality of clinical operations quantity.

(4) Risk communication and reporting

All functional departments should collaborate with each other to analyze and summarize the collected information on a regular basis.

summary, including the variability assessment of the test data itself and its relevant time collection points,
Assessment of exceeded QTL or protocol deviations, assessment of missing data, etc. OK
to drill down within and across centers on single or multiple indicators
Statistical analysis to obtain more information. Any trend analysis should be done in conjunction with the overall
Scientific value and data availability, and corresponding priority and risk levels
relevant, and should be combined with information from on-site inspection reports and data management reports.
information. All parties need to communicate in a timely manner throughout the clinical trial to ensure the disclosure of information
and transparency, all important quality management measures should be documented and documented from
And better support risk assessment and control.

After the clinical trial is completed, qualitative and quantitative summaries of the QTL results should be summarized.
implementation within the scope, this information can be summarized in clinical study reports (data
Quality Assurance Chapter). All risk indicators related to the QTL should be presented
In the report, regardless of whether the indicator value exceeds the QTL. If the number of risk indicators
If the QTL value exceeds the set QTL, the clinical research report should also report its safety to the subjects.
Potential impact on safety and test data reliability, and cause analysis and description
measures taken.

3. Statistical application in centralized supervision

Risk-based quality management is a combination of on-site and centralized monitoring
The dynamic clinical trial management process can continuously improve the quality of trial implementation.
Throughout the risk-based monitoring process, centralized monitoring should be properly implemented, especially
It is the rational use of statistical methods that can further improve the effectiveness of on-site monitoring.
efficiency. Statistical methods and models can be used in centralized monitoring to check and

Manage the trial process and collected clinical data to identify atypical data

Patterns or abnormal trends to achieve the following purposes:

- Monitor the overall quality of the trial at the trial level and identify possible effects on subjects

  Systemic issues with safety or reliability of test results;

- At the research center level, conduct comparisons between centers to identify potentially high

  Risk center to determine the goals and extent of on-site monitoring;

- Assess data quality at the test data level and check test data consistency

  and completeness to determine whether there are systemic problems in the data collection process,

  Obvious errors or data authenticity issues.

(1) Common statistical indicators for centralized monitoring

ICH E6 (R2) recommends setting risk indicators and their QTL at the experimental level.

Trial-level risk indicators and corresponding QTL can be carried out for a certain trial

Specifically set, there are some risk indicators that may apply to all clinical trials by a sponsor.

clinical trials and defined in the sponsor's quality system. Experimental level risk indicators

The number of subjects should not be too large and should be selected with complete coverage of subject rights and trial data.

indicators closely related to sex. Commonly used indicators include enrolled subjects not meeting

The proportion of inclusion criteria, the incidence of serious protocol violations related to trial drugs,

The proportion of subjects whose primary or key secondary endpoints could not be observed, etc.

Similarly, for key data and key processes, you can also

Set center-level risk indicators on a unit-by-center basis and use the data from a single center level

Statistics calculated to judge the performance of a center. Risk indicators at trial level

Standards can generally also be used at the center level. Common center-level risk indicators

Including enrollment rate, screening failure rate, case report form completion time, data

Question rate, question resolution time and number of active questions, (serious) defects

Number of events, number of missing or delayed follow-up visits, number of protocol violations, etc.

Risk indicators at the center level also need to match and define corresponding thresholds. in single

When the index value of the heart exceeds the threshold, corresponding measures are triggered (for example, strengthening the data

review, increase on-site inspections, etc.). The choice of threshold will be affected by many factors

influence, including the purpose of the experiment, experimental design, type of indicators, different locations

District/centre differences etc. Therefore, statisticians need to work with other teams based on

The specific circumstances of the experiment determine how the threshold is defined.

Based on the inspection of test data quality and authenticity, the above equipment can be

It can be carried out based on risk indicators at a certain trial level or center level, or it can

Use non-critical data (e.g., baseline characteristics, concomitant treatments, etc.)

The contents of periodic centralized monitoring are determined to determine whether there are abnormal data patterns.

(2) Statistical methods commonly used in centralized monitoring

The choice of statistical methods should serve the specific monitoring purpose. The following introduction

are statistical methods that can be referenced in centralized monitoring. Sponsors can use

Choose an appropriate method based on the characteristics of the experimental design and data.

1. Statistical methods at the experimental level

To monitor the overall quality of the trial, discover possible effects on subject safety, or

When the purpose is to solve system problems or the reliability of test results, the selected wind can be used.

The summary value of risk indicators at the trial level is consistent with the preset values before the trial starts.

QTL comparison. The setting of QTL can refer to historical data and consider indicators

medical and statistical characteristics, and the statistical design of the trial. QTL can be set

Set lower or upper limits, or both, and narrower warnings can be set

Threshold, the upper or lower limit of the early warning threshold should be within the QTL range to serve as an early warning

and the role of early intervention.

Comparing the value of the risk indicator with a threshold (QTL or warning threshold) can

It can also be used to simply judge whether it is greater than or less than the upper and lower limits.

Preset statistical inference methods, such as hypothesis testing, interval estimation, Baye

Sifa et al.

2. Statistical methods at the research center level

Identify high-risk research centers to determine the focus and extent of on-site inspections

For this purpose, the method of comparing the values of risk indicators and thresholds at the experimental level mentioned above is

The method can be applied at the central level, or statistical methods of outlier detection can be used.

Methods can be used to compare centers to identify potential high-risk research centers. This type of method

It is assumed that centers participating in the same study follow the same study protocol for subject screening.

selection, treatment, and evaluation, so there is a large degree of similarity, as shown in

Risk indicators at the center level should follow the same distribution. When a center interacts with other

When a center's performance is significantly inconsistent and its risk indicator values become outliers,

It indicates that the center may have potential quality risks. Setting and comparing thresholds

It can be the incidence of adverse reactions among subjects in one center and the

Is the difference in the ratio outside a certain preset percentage range; or is it within a certain statistical range?

Under the model, the index value of a center is distributed among all centers after normalization.

whether it is outside a preset quantile; and test whether the center indicator is consistent with

Whether the *P* value of the co-center indicator difference is less than a certain preset test level, etc.

When comparing between centers using summary values of risk indicators at the center level,

It is necessary to consider the differences caused by the different number of patients enrolled in the center or the follow-up time.

the same degree of uncertainty. Even under the assumption of homogeneous risk, the number of patients

Centers with lower volumes will have greater variability in risk estimates than centers with greater

bigger. If the sample size is not considered and a single center is compared directly with the whole,

Whether using absolute values or relative proportions of differences, the focus may be

Focus on centers with smaller sample sizes. When risk indicators are related to follow-up time,

For example, the number of adverse events is related to patient years of exposure, and the follow-up time is also

It will bring about differences in the variation of risk indicators. Commonly used processing methods include funnel charts,

Each center is evaluated using multiples of the standard deviation as a threshold; it can also be

Hypothesis testing, comparing a certain center with other centers, the smaller P value indicates

identify potential outlier centers; you can also consider Bayesian methods, using Bayesian collection

The shrinkage estimator handles differences in center size. In addition, when using multiple risk indicators

When conducting inspections on standards, attention should be paid to multiple issues and appropriate control methods should be selected.

False discovery rate. These methods can identify individual risks at a central level

Potential outliers of indicators serve as guidance for on-site inspections, reminding inspectors that they should

Pay more attention to the corresponding abnormal indicators.

Sometimes it is also necessary to be able to combine multiple risk indicators to obtain a reflection of the central quality

Comprehensive score of quantitative risk. At this time, the weight can be calculated based on the preset weight.

There is a weighted average of the indicators, or the decision is based on the correlation matrix between indicators.

To determine the weights, other multivariate statistical methods can also be used (e.g., Mahalanobis distance

distance, using Euclidean distance based on partial principal components after principal component analysis, etc.).
This composite score (distance) measures the distribution of each center's data relative to the study's overall
degree of difference. Higher scores (further distance) indicate greater outliers.
Therefore, such a score can be used as an overall measure of a center's quality risk, using
To determine the frequency and urgency of on-site monitoring.

3. Centralized monitoring of test data

In order to find systematic problems or errors in the data, including systematic testing
measurement error (for example, using an uncalibrated instrument), or incorrect data entry.
errors, omissions, or authenticity issues, etc., in addition to targeting key data and
Statistical analysis can be carried out on key processes and can also be carried out on some non-key data.
Analyze and discover its abnormal patterns. The choice of statistical methods and the aforementioned findings are highly
The Risk Research Center's approach is similar. In addition, for univariate data, you can check
Check descriptive statistics such as mean, variance, kurtosis and skewness of a single central variable
Indicator, by comparing whether it is in the standard of corresponding indicators in other centers
Differential multiples are used to find outliers; it can also be used with visual graphics (for example,
Histogram, stem-and-leaf plot, boxplot, etc.) to find outliers. For multiple consecutive
type variables, you can test the correlation coefficient matrix sum of these variables at the central level
The consistency of the correlation coefficient matrix at the experimental level is used to determine whether there are abnormal numbers.
according to. Alternatively, you can analyze the distribution of endpoint numbers in the results or examine their
Randomness (for example, using methods such as volcano plots or Benford's law) to identify
Whether there is an issue with data authenticity.

For dynamic continuous monitoring based on accumulated data, process control can be considered

statistical tools (e.g., control charts) that plot variables as they accumulate numbers

Distinguish random fluctuations and abnormal fluctuations based on changing trends to determine the system's

stability and take timely measures to eliminate system abnormalities.

4. Centralized Supervision Plan and Report

Risk-based quality management in clinical trials usually revolves around the following links:

Conduct risk assessment by collecting information and identifying key data and processes; implement

Risk control, including setting risk indicators and QTL at the trial level and central level

Risk indicators and thresholds, etc.; combined with the information collected in the previous steps, experiments

New information emerges during this period, and risk management tools are useful for discovering risks related to

Communicate the results and data in a timely manner to determine the measures that need to be taken.

All clinical trials may have issues with data integrity, patient safety and

Program Adherence and Compliance Risks. Based on the concept of quality by design, Pro

Monitoring should be carried out systematically in accordance with a risk-based approach in bed operation management.

Including on-site inspection and centralized inspection. The centralized audit plan is conducted centrally

It provides the basis for chemical monitoring and provides a systematic plan for regular review of data.

The centralized audit plan requires a centralized audit team composed of cross-departments.

Written and executed together. Statistics should focus on, but not limited to, the monitoring plan

Formulation, determination of key data and processes; selection of centralized monitoring methods;

Monitoring time, type, frequency and extent determined according to test characteristics; trigger

Standards for adjustment of monitoring activities, etc. The monitoring plan can be based on the actual situation

Adjustment.

The centralized monitoring plan should first clarify the risk indicators based on the plan.

The determination of indicators is usually synchronized with the risk management plan and should be done before the first subject Complete before joining the group. When risk indicators are determined, corresponding thresholds also need to be set. At the same time, attention should be paid to the time point from which to start risk assessment, because the test The early stage may not be fully representative because of the small number of enrolled people. also, The frequency of data reviews should also be stipulated in advance.

After setting the risk indicators, you can formulate corresponding risk indicators based on this information. Chart templates, and generate corresponding reports based on preset time frequencies to facilitate The centralized monitoring team conducts regular reviews to monitor the quality of clinical trial operations. Timely and effective monitoring. The review results need to be recorded in the centralized monitoring report and filed files. Review of risk indicators at the trial level is particularly important if the values exceed The QTL threshold needs to be recorded in detail and started with the quality audit department. Cooperate in investigations and implement corrective and preventive actions when necessary.

5. Other considerations

Centralized by cross-departmental collaboration based on overall clinical data Monitoring can detect systemic problems in a timely manner and improve the credibility of test results. Although the statistical methods used may be more complex, since they are not specific Do not rely on the selection of subjective indicators or the setting of thresholds. Therefore, it is necessary to have a certain universality. With similar structured data, a statistical program or system device can be reused in different trials, as can monitoring results from similar studies for comparison. What needs to be made clear is that data review in centralized monitoring is different. In the interim analysis, the design of charts in the centralized monitoring plan serves the purpose of monitoring the Overall risk signals from clinical trials rather than safety and/or efficacy data

Statistical analysis, especially to avoid breaking the blind. When a specific risk is detected

signal, it may be necessary to conduct in-depth analysis of the data to determine clinical operation

Are there any systemic risks in the camp, or even data authenticity issues. when necessary,

It is recommended to communicate with the regulatory authorities.

6. References

[1] ICH. ICH E6(R2): Good Clinical Practice: Integrated Addendum to ICH E6(R1) (2017).

[2] ICH. ICH E8(R1): General Considerations for Clinical Studies (2021).

[3] I. ICH Q9: Quality Risk Management (2006).

[4] FDA. Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring (2013).

[5] FDA. A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry (2019).

[6] EMA. Reflection paper risk based quality management clinical trials (2013).

[7] State Food and Drug Administration's "Good Clinical Practice Practice for Drugs" (2020).

[8] ICH. E9(R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials to the Guideline on Statistical Principles for Clinical Trials (2019) .

[9] Bhagat R, Bojarski L, Chevalier S, et al.Quality Tolerance Limits: Framework for Successful Implementation in Clinical Development. Therapeutic Innovation & Regulatory Science, 2021, 55(2): 251–261.

[10] Zink RC, Dmitrienko A, Dmitrienko A. Rethinking the Clinically Based Thresholds of TransCelerate BioPharma for Risk-Based Monitoring. Therapeutic Innovation & Regulatory Science, 2018, 52(5): 560–571.

[11] Trotta L, Kabeya Y, Buyse M. Detection of Atypical Data in Multicenter Clinical Trials Using Unsupervised Statistical Monitoring. Clinical Trials, 2019, 16(5): 512–522.

[12] Bottle A, Aylin P. Statistical Methods for Healthcare Performance Monitoring. CRC Press, 2016.

[13] Hu Jin, Xu Yan, Zhou Gaochao, et al. Optimizing anti-resistance through centralized monitoring based on risk assessment statistical model Oncology drug clinical trial quality management. China Food and Drug Administration, 2021.

[14] Shwartz M, Ren J. Estimating a composite measure of hospital quality from the Hospital Compare database: differences when using a Bayesian hierarchical latent variable model versus denominator-based weights. Medical care, 2008, 46(8): 778–785.

[15] Spiegelhalter D, Sherlaw-Johnson C, Bardsley M. Statistical Methods for Healthcare Regulation: Rating, Screening and Surveillance: Statistical Methods for Healthcare Regulation. Journal of the Royal Statistical Society: Series A (Statistics in Society), 2012, 175(1): 1–47.

[16] Benford F. The law of anomalous numbers. Proceedings of the American philosophical society, 1938, 551–572.

Appendix: Chinese and English comparison table

Chinese	English
Bayesian Shrinkage Estimator	
false discovery rate	False Discovery Rate, FDR
Electronic Case Report Form, eCRF	
critical quality factors	Critical to Quality Factors
Corrective and Preventive Action,	
	LAYER
Control Charts	Control Chart
Mahalanobis distance	Mahalanobis Distance
Euclidean distance	Euclidean Distance
On-site inspection	On-site Monitoring
Warning threshold	Secondary Limit
Centralized monitoring	Centralized Monitoring
Quality Tolerance Limit, QTL	