annex

Clinical trial data management technology Guide

I. Overview

Clinical Trial Data quality is evaluated on the basis of clinical trial results. In order to ensure accurate and reliable results of clinical trials, scientific credibility of the international community and countries in the world have issued a series of rules, regulations and guidelines to regulate the management of clinical trial data of the entire process. Meanwhile, the progress of modern clinical trials and the development of science and technology, especially the development of computer, network and clinical trials and data management standardization provides a new technical support, also contributed to the Governments and the international community to actively explore the clinical test data management and standardization of new models.

(A) domestic regulatory status of clinical trial data

China's "Good Clinical Practice" (Good Clinical Practice, GCP) clinical trial data management requirements put forward a number of principles, but regulatory and technical provisions on specific data management operations is still in the blank. Due to the lack of supporting technical guidelines, our degree of standardization in the pharmaceutical clinical trial data management is not high, clinical trial data management quality varies greatly, thereby affecting the objective scientific evaluation of the efficacy and safety of new drugs. In addition, the domestic clinical trials, development and application of electronic data management system is still in its infancy, clinical trial data management patterns are largely paper-based case report forms (Case Report Form, CRF) data collection phase, electronic data acquisition and data management system to be the promotion and popularization. At the same time, due to the lack of national data standards, it is difficult to do a similar study between database information sharing.

(Ii) International Clinical Trial Data Management Overview

Internationally, people use drugs Technical Requirements for Registration International

Conference on Harmonization of clinical study drug quality management practices (hereinafter referred to as ICH E6 GCP) for clinical trial data management has a principled requirements. For researchers to carry out clinical trials, research and record manufacturers and responsibilities related to the testing process, the source data, verification and so on, directly or indirectly made a principled provisions to ensure that all types of data obtained in clinical trials true, accurate, complete and reliable.

States have enacted relevant laws and regulations and guidelines provide specific evidence and guidance for the standardization and regulation of clinical trial data management. Such as: (21 CFR Part 11) Electronic Records and Electronic Signatures rules of clinical trial data, 21 CFR Part 11 (1997), making electronic records, electronic signatures with the traditional handwritten records and handwritten signatures have the same the force of law, so that the US food and Drug Administration (FDA) to accept electronic clinical research materials. Accordingly, the FDA made clear requirement in August 2003 issued a corresponding technical guidelines, the provisions of Part 11 of the

made specific interpretation and validation of computer systems, inspection track record and file copying and so on.

In May 2007, "Guiding Principles of clinical trials using a computerized system," issued by the US FDA (Guidance for Industry: Computerized Systems Used in Clinical Investigations) for clinical trials in the development and use of computer systems to provide a basic reference standard .

And clinical trial data management by the International Society of relevant experts in the field (Society of Clinical Data Management, SCDM) also formed a "good clinical data management practices" (Good Clinical Data Management Practice, GCDMP), the file is clinical each key test data management had established a minimum standard corresponding operation and the highest specifications, providing specific technical guidance for practical clinical trial data management.

In summary, the international community and the developed countries have established a number of clinical trial data management regulations, regulations and technical guidelines in order to ensure the quality of the test data. And in this regard

China started late, slow development, clinical trial data management standardization owe a direct impact on our drug discovery and supervision. Current national strategic plan of building an innovative society requires special programs and major new drug clinical trial data management standardization made more urgent needs. In view of its importance and urgency, in a positive summary of the current level of technology and research and development trend of clinical trial data management, based on the particular formulation of the technical guidelines.

This guide from the requirements of data management responsibilities related to personnel qualifications and training, management systems, standardized test data, the main contents of data management, data quality assurance and assessment, as well as six aspects of data security and serious adverse events comprehensive interpretation aimed at data management of clinical trials to play the role of standardization and guidance, applicable to the registration of drugs for the purpose of clinical trials, post-marketing clinical trials and for other types of tests are also instructive.

Second, the responsibility for data

management related to personnel qualifications and training

Clinical trial data management requirements for clinical trials research project team effort and full cooperation. Research and data management staff involved in work-related sponsors, investigators, auditors, data administrators, and contract research organizations (Contract Research Organization, CRO) and the like.

Liability (a) the relevant personnel

1. Sponsor

The sponsor is to ensure the quality of clinical data ultimately responsible. The sponsor should develop quality management evaluation procedures, quality management plan and operational guidelines, and should establish inspection department, the sponsor can audit their own when necessary, quality system compliance systematic inspection by personnel not directly involved in the test on a regular basis. In addition, the sponsor should ensure data integrity, and compliance with supervisory responsibility for the data management process, compliance, and data quality of CRO including outsourcing when appropriate work

supervision.

The sponsor of a default in the data management aspects, for example: researchers untrained and fill in the CRF; research programs is not clear or unreasonable.

2. Researchers

Researchers should ensure that CRF or other form of a report to the sponsor's data is accurate, complete and timely, and should ensure that the data on the CRF from the source data records on the subject, and must be given for any different interpretation of them.

Researchers error in the data management aspects / misconduct example: violation of the study protocol, such as the wrong time to visit; the source CRF data entry errors; laboratory instruments artificial measurement error; fill in the CRF does not have the qualified personnel; researchers fraud.

3. auditors

Inspectors should be based on the data source document verification CRF, once you found an error or difference shall notify the investigator, and according to errors or discrepancies found, record the appropriate question to ensure that the recording

and reporting of all data correctly and complete.

CRA common problems, for example: no original medical or original medical records no records (missing or incomplete); CRF fill vacancies in errors or irregularities; recording adverse events is incomplete; unreported suspected fraud to the sponsor; test The results can not be traceable (laboratory data, ECG, X-ray films, etc.).

4. Data Administrator

Administrators should follow the data requirements of the research program, in the design of CRF, to establish a database of data management standards and establish inspection procedures and test logic. After receiving CRF, CRF entry personnel to make checks on entry before; after CRF data is entered into the database, the use of validity, consistency, and lack of the normal range logic test program to check the data and the like. Data administrators discovered the problem should be cleared up, data issued by the investigator questioned (Query) be resolved.

Data administrators should participate in clinical investigator meetings for the study team timely and effective measures to improve and enhance the

quality of data.

A default data administrator Example: CRF table design does not meet program requirements; logic test program error; described in language in question has induced ingredient; in the wrong question to update the database.

5. Contract Research Organization (CRO)

ICH GCP may be noted that the sponsor of clinical trials related work and tasks entrusted to part or all of a CRO, but the ultimate responsibility for the quality and integrity of the trial data always sponsor. CRO should implement quality assurance and quality control.

The sponsor should first clarify the scope of data management outsourcing, if you plan to outsource the management of data, then the next step is to choose the right CRO, CRO cope with the candidate's qualifications and ability to evaluate.

Evaluation CRO should consider the following factors: CRO qualifications, past performance and its ability to perform the contract; quality control, quality assurance processes; authentication data management systems and facilities; data management SOPs (Standard Operating Procedure,

SOP) and proof of compliance with SOP; staff qualifications, to grasp the situation of the SOP and training records; record document change control process; a file storage system.

Upon election, the sponsor and CRO will sign a valid contract, the two sides in the contract with explicit responsibilities, rights and interests. Trial sponsors to respond when necessary CRO-related training to ensure that the services they provide meet the sponsor's quality standards. In the clinical trial data management process, the need for trial sponsors activities carried CRO timely and effective management, communication and verification, in order to ensure compliance with mutually agreed process requirements. Sponsor's quality management plan must include CRO quality control information, and the process must be clear and expected results.

Qualification and Training (ii) data management staff

Responsible for clinical trial data management must go through GCP, professional training relevant laws and regulations related to SOP, and data management to ensure its proper qualifications with

job requirements.

Data management professional training shall include, but are not limited to: Data Management SOP and sectoral policies; standardization of clinical trial data and document archiving rules; training data management systems and related computer software applications and operating capacity; regulations and industry standards: GCP , CFDA regulations and guidelines, and ICH guidelines; confidentiality, privacy and data security training.

Data managers must preserve the integrity of training records for verification, training records required course name, date, name of the trainer, course, completion status, trainees and their supervisors signature. If it is web-based training system should provide proof of training, indicating the name of the course, trainees names, as well as training time to complete.

Data managers should also accomplished through continuing education and improve professional quality, to ensure high-quality data management.

Third, the clinical trial data management system

The importance of (a) clinical trial data

management system

Objective data management is to ensure that the data is reliable, complete and accurate. Data management process including the collection / management system is established, the design CRF and database data receiving input, data verification and questioning, medical coding, external data management, blind review, database locking, data export and transfer of data and data management documents the archiving. Object data management is to achieve high-quality real data. Thus, the various stages of clinical trial data management needs to run in a complete, reliable clinical trial data management system, clinical trials project team must establish a management system in accordance with the principles of science, namely, data management systems, data may affect the quality of the results various factors and aspects of full control and management of these factors are under control, so that clinical research data is always maintained in a controlled and reliable level. Data management system here does not mean the narrow sense of the computer system, but a generalized data quality management system (Quality Management System,

QMS), which is an integral part of the clinical trial project management system.

The establishment and implementation (ii) the data quality management system

Establish a data quality management system is the application of scientific management, improve the management level, the process of evolving.

The establishment and implementation of quality management system first need to establish quality policy and objectives, in order to determine the expected results, helping managers to use its resources to achieve these results. Quality is quality objectives and direction of managers, quality objectives are specific policy, a manager in the quality of the objective pursued.

Quality management systems rely on the organization to coordinate and run, we must establish the organizational structure of a quality management system to adapt. Organizations should be clearly defined responsibilities and authority data management-related personnel.

Implementation and operation of the quality management system through the establishment of implementing the quality management system file to achieve. Quality management system

documentation generally consists of four parts: quality manual, procedures, work instructions, quality records. Quality Manual is the core quality policy objectives, organizational structure and quality system elements of description; program files is complete the quality of activities of method made provisions; operating instructions is to provide a particular job specific operating procedures of files, data administrator is commonly used "operating Manual" or "rules," and the like; quality records for completed activities or results achieved provide objective evidence file.

After completion of the quality management system documents, over a period of trial operation, testing the applicability and effectiveness of these quality management system documents. Data management agencies through continuous coordination, quality control, information management, quality management system audits and management review, to achieve the effective operation of the quality management system.

Establishment of data quality system management, implementation and operation is a dynamic process, the most important is the data management requirements related to quality

management personnel to implement the concept into the daily work of data management.

(Iii) the basic requirements of clinical trial data management system

1. System Reliability

System reliability is the ability of the system under specified conditions, within the specified time, to achieve the specified functions. Clinical trial data management system must be based on a consideration of the risks, in order to ensure data integrity, security and credibility, and reduce the possibility of problems due to system or process generates an error.

Computerized data management system must be rigorous design and verification, and form validation summary report to verify the need to prepare regulatory agencies, which prove the reliability of management systems.

2. Clinical trial data traceability

The clinical trial data management system must be provided with traceability (Traceability) performance for the clinical trial data. CRF data should be consistent with the source file, any discrepancy should be explained. Any changes or corrections should be dated, signed and explain why

the name of CRF in the data (if necessary), and shall make the original record is still visible.

Track inspectors clinical trial data (Audit Trail), from the first data entry as well as every change, deletion or addition, must remain in the clinical trials database system. Date of inspection should include changing the trajectory, time, change the people, change reasons, the data value before the change, the changed data values. This track inspection system protection, does not allow any artificial modification and editing. Inspection records should be kept on track and query.

3. Rights Management Data Management System

The clinical trial data management system must have complete rights management system. Paper-based or electronic data management are required to develop SOPs control permissions (Access Control) and management. Grant different rights to the data management system in different people or roles that only authorized personnel are allowed to operate (record, modify, etc.), and shall take appropriate methods to monitor and prevent people not authorized to operate.

Electronic Signature (Electronic Signature) is a means of electronic management system permissions management. For electronic management system, each user of the system should have a personal account, the system requirements before you begin operating data to be logged in account, quit the system after completion; users can work with their password, the password can not be shared, nor let others access login; password should be changed periodically; when you leave your workstation and terminate the connection to the host computer is idle for a long time to implement disconnect itself; a short pause when work should have automatic protection procedures to prevent unauthorized data operations, such as the use of protective measures in front of the screen to enter the password.

Fourth, standardized test data

Clinical trial data standardized meaning is: a standardized data format is the basis of clinical trial data management system and the clinical trials of medical institutions to establish interoperability information; establish a seamless data exchange between different studies internal sponsor, and the sponsor between communication, communication

between the sponsor and the drug review mechanism to facilitate; facilitate clinical trials for each drug safety data sharing; easy to inspect the metadata (meta data) storage and regulatory authorities, between different systems and application programs data integration provides a unified technical standards; facilitate the review mechanism, so as to shorten the approval cycle; helps to enhance the quality of data, we can provide higher quality data faster.

(A) CDISC

CDISC (Clinical Data Interchange Standards Consortium) is a global, open, multidisciplinary, non-profit organization, established to cover study design, data collection, analysis, exchange, submission and other aspects of a series of standards. CDISC core criteria below.

standard	description
List of research data model (SDTM)	The clinical study case report form data standard for content submitted to the regulatory standard.
Analysis Data Model (ADaM)	Data collection and analysis related to the basic principles and metadata standards, standards for content submitted to the regulatory authorities.
XML technology (ODM, Define-XML and Dataset-XML)	Operational Data Model (ODM) is an XML-based summary describes how to comply with regulatory requirements, acquisition, exchange and archiving of clinical data and metadata. Define-XML based metadata standard ODM description of research data sets. Dataset-XML is based on XML Schema described ODM description of research data sets.

Controlled set of terms (CT)	Supports standard vocabulary and coding set CDISC models / standards involved.
Harmonized standards (CDASH) clinical data acquisition	Content for standard case report form the basis of the data collection field.
Laboratory Data Model (LAB)	Room describe the clinical and laboratory research sponsor / CRO Get in touch with the description of the content standard for exchanging clinical laboratory data rules.
Non-Clinical Data Interchange Standards (SEND)	Description standard preclinical study data.
Programme Presentation Model (PR)	BRIDG based model to describe the tools in clinical research program elements and relationships.
Therapeutic area data standards (TA)	A set of standards on concepts and study endpoints such as target therapeutic areas determined to improve semantic understanding, support data sharing, ease of global registration submission. Such as Alzheimer's disease, cardiovascular disease, diabetes and so on.

International regulatory bodies such as the United States developed FDA, Japanese Pharmaceuticals and Medical Devices Agency (PMDA) will force required to submit electronic data meets CDISC standard CDISC standards have seen more and more recognized and widely used in the industry, has become an international clinical trial data "common language."

To improve the quality and efficiency of clinical trial data quality and statistical analysis, to facilitate the exchange of data and meta-analysis, when the new drug application for registration is recommended CDISC standard to submit the original

database and the database analysis.

(B) the medical terminology standards

1.MedDRA

MedDRA medical terminology used as drug registration set, all safety reports and medical diagnostic products suitable for registration under the jurisdiction of the government. In clinical studies, spontaneous reports of adverse reactions, the report registered by the government registry of product information are required to use MedDRA.

MedDRA contains five terms, which are system organ class (System Organ Class, SOC), a high-level set of terms (High Level Group Term, HLGT) , the high-level terms (High Level Term, HLT), the preferred term (Preferred Term, PT) term and low-level (low level term, LLT).

2. WHO Drug Dictionary

WHO Drug Dictionary for pharmaceutical products is the most comprehensive electronic dictionary, the WHO International Drug Monitoring program an important part. WHO Drug Dictionary using anatomy, Therapeutic Chemical Classification System to classify the drug, commonly used in clinical trials in combination therapy reports,

post-marketing adverse reaction reports and other sources of drugs mentioned in the report is encoded and analysis.

WHO Drug Dictionary includes 4: WHO Drug Dictionary (WHO DD), WHO Drug Dictionary Enhanced Edition (WHO DDE), World Health Organization herbal dictionary (WHO HD) and integrated dictionary (Combined Dictionary).

3.WHOART glossary

WHOART is a higher coding accuracy and medications during the term set for clinical information, covering almost all the necessary medical terminology adverse reaction reports, can be printed out in the form of a list of rows. Because of new drugs and new indications will have adverse reactions term, term set flexible structure, allowing the incorporation of new terms while retaining the term set structure, without the relationship between terms before losing.

WHOART contains four terms, namely, the system organ class (System Organ Class, SOC), senior term (High level term, HT), preferred term (Preferred Term, PT) and included in the term (Included terms, IT).

Fifth, the main content data management

Before clinical trial data management, data management plan must be developed (Data Management Plan, DMP) by the data management department under the actual project. Data management plan should include the following time points and data management and related personnel responsibilities clear. Data management, data management plan should be signed by the sponsor and execution.

(A) CRF design and fill

1.CRF Design

Clinical trials mainly dependent on various clinical trial data collected CRF is produced during the test. CRF must be designed to ensure that the test program was to collect all the required clinical data (except for external data). Design, production, version control and approval processes CRF must be fully documented.

CRF design, edit, and final confirmation will involve participation in multi-party personnel, and may include the sponsor, the sponsor commissioned CRO, researchers, data management and statistical personnel. Generally, CRF first draft completed by the

sponsor or CRO, but its modification and improvement participation by the parties, must ultimately be approved by the sponsor.

2.CRF fill Guide

CRF guide is based on research programs to fill the page table and each data point of the case report form to fill specific instructions.

Guidelines for completing the CRF can have different forms and can be applied to different types of CRF or other data collection tools and approaches. For the purposes of the paper CRF, CRF should be part of the guidelines for completing the CRF or a separate document printed. For EDC (Electronic Data Capture) systems, the guidelines for completing it may be the instructions for the form, online help, and the system prompts the dialog box for entering data generated.

Ensure clinical trial centers in selected subject obtained prior to its guidelines for completing CRF, and relevant staff clinical trial centers program, CRF completion and submission of the data of the training process, the process takes archival records.

3. Notes CRF

Note CRF CRF is blank label, recording the

location of each data item and CRF variable names and coding in the corresponding database. Each CRF All items need to be noted, is not entered into the database of data items should be labeled as "not entered into the database." Note CRF as a link between the database and the CRF to help data managers, statisticians, programmers and drug evaluation bodies in understanding the database. Note CRF can be manually marked, electronic technology can also be used to automatically label.

4.CRF fill

Clinical investigator information must be accurate, timely, complete, standardized fill in CRF according to the original data. Revise CRF data must comply with SOP, subject to change marks.

Design (b) of the database

Clinical trial design diversity, data collected for each research project depends on the clinical trial program. Clinical trials should ensure the integrity of the database, and try to comply with the structure and set the standard database, including the names and definitions of variables. On specific research projects, the establishment of the database should CRF of the project is based on the data set name,

variable name, variable type and variable rules should be reflected in the comments CRF.

After the database is created, the database should be tested by the data management and signed by the person in charge.

(Iii) receives input data

Data can be received through a variety of ways, such as fax, mail, security measures have traceable courier, inspectors personally passing, network entry, or other electronic means. Data receiving process should be a corresponding file records to confirm whether the data source and receiver. Should submit the data center have procedures to ensure confidentiality of the subject identification information.

Data entry process must be clear that the test data entry requirements. Data entry process generally include: double double entry, single entry with manual review, and the use of EDC direct way.

(Iv) data verification

Purpose is to ensure the verification of data integrity, validity and accuracy of the data. Before data verification, it should be listed detailed data verification program, data verification including but

not limited to the following:

Determine the original data is correctly and completely entered into the database: check for missing data, find and remove duplicate data entry, check the uniqueness of certain values (such as subject ID);

Randomization Verification: In a randomized controlled trial, check the randomization implementation;

Contrary to the verification program: According to clinical trial program to check the subject inclusion / exclusion criteria, test plans and drug combination therapy (or therapy) and other provisions;

Time window Verification: verification sequence between the groups, follow-up date to judge compliance situation;

Logic Verification: Logical association between the respective events to identify possible data errors;

Range Verification: identification impossible in the physical or extreme values outside the normal range of variation of the study population;

Consistency Verification: verification of consistency between such serious adverse events and clinical safety database database, external data

and CRF data collection consistency verification, verification and other medicine.

Primary and secondary indicators of effectiveness data management response program specified in the key safety indicators to ensure adequate verification of the correctness and completeness of the data.

Data verification test should be grouped under unknown circumstances, question the data table contents should be avoided or induced bias question, the results of induced or forced to answer questions will test there are deviations.

Data verification can be manually checking and verification of computer programs to achieve. Data verification procedure should be diverse, each clinical researchers have a responsibility to use different tools involved in clean-up database queries from different angles.

Sometimes, the simple logic and can clear error of judgment defined in advance, the researchers obtained consent in data administrator data can be revised in accordance with prior regulations, and track record in the audit.

(V) data management challenge

Question arising after verification of data sent to

the CRA or researchers in the form of electronic or paper documents. After the researchers question to answer, according to the data administrator replies to queries return the data to be modified. Such as the unresolved question with a new question will be re-issued until the data is in doubt clean.

Record (vi) data changes

Incorrect data in the data clean-up process will be corrected, but it must be done through question / answer mode, even if approved in a conference call data changes.

Data management process to keep a full record of the questioning process.

(Vii) Medical Coding

History collected in clinical trials, adverse events associated with treatment recommendations using standard pharmaceutical encoded dictionary. Encoding process is to describe a standard dictionary to collect from the CRF in the entry word matching process. Medical coders must have the clinical knowledge and understanding of the standard dictionary. When it appears Words can not match directly with the dictionary can be hand-coded, for medical coders can not confirm the

entry word should be challenged by the data communication with the researchers to obtain more detailed information to make more precise coding . Medical coding should be completed before the lock library.

Widely used standard dictionary have MedDRA, WHO Drug, WHOART. Data management should formulate SOP, and to ensure timely update the dictionary of medical and drug coding consistency between the different versions of the dictionary. Dictionary name and version information should be used in clinical research data management plan description explains.

CRF changes modify the (eight) protocol

Of the pilot program to modify the drug in clinical trials sometimes occur, but not all of the test program modifications are needed to change CRF, the need to develop appropriate procedures to deal with such situations. CRF should be noted that important changes should be given institution / Institutional Review Board (IRB / IEC) for approval before the entry into force of the revised program.

(Ix) Laboratory and other external data

In the organization and implementation of the

clinical trials process, there are provisions in the acquisition of some clinical trial program, but the research base outside researchers obtained external data provided by other vendors (such as the Central Laboratory). External data detection equipment (such as blood chemistry, ECG, blood analyzer, monitoring of vital signs; laboratory data, pharmacokinetic / pharmacodynamic data, biomarker detection data and the like: external data type such as: biological sample analysis data subject record;, imaging, etc.).

The following aspects could affect the integrity of the external data, during the establishment of a database should pay attention to: the definition of key variables and required content; data editing and verification procedures; record format and file format (for example, SAS, ASCII); data transmission; database update; data storage and archiving.

Care must be taken to ensure that sufficient information is available for the identification and processing of external data, selection of key variables (uniquely describe each sample recorded data). Without key variables will be patient, samples and visits with the results recorded accurately

matching difficult.

Usually local laboratory data collected by manual entry, to be concerned about the differences between the various laboratory units and their normal range, the emphasis on inspection of missing data, outliers, and duplicate data and the like. Laboratory data collection centers mainly transmitted through electronic file format. Before the study began, the data administrator to develop a detailed protocol for the transmission of data center laboratory, the structure, content, transmission, transmission time, and workflow and other external data for specific technical requirements.

Administrators should be timely data on external data verification, inspection procedures such as application logic, make the appropriate checks and review of the medical association and the like, and start questioning the problems found.

For the problem of verification laboratories and other external data found in clinical studies inspectors want to make 100% of the data source data verification.

(J) the data blind review

Whether the clinical trial process is open or blind operation before clinical trials database

locking, by sponsors, investigators, data management and statistical analysts blinded common final audit data does not solve the problem, and in accordance with the clinical pilot program for statistical analysis population division, serious adverse event reporting and verification of handling of records.

Such as double-blind clinical trials need to check the mail and emergency unblinding total blind clinical trial whether the bottom seal intact, if emergency unblinding occurs, the need for emergency unblinding reasons and processing reports.

(Xi) database locks

Database locking is a clinical study is an important milestone. It is a database editor permissions on the database documents inadvertent or unauthorized changes, and in order to prevent cancellation. Database locking process and time should be clearly documented, for blinded clinical trials database before they can lock unblinding.

Listing 1. Database locking

Before locking the test database after the database is locked, the lock should be pre-established procedures and strict adherence to

the library, they should inform the relevant staff to ensure the testing and approval of all relevant personnel.

Data Administrator shall establish a list of database locks, locking the database list of suggestions including but not limited to, the following: All data have been received and properly entered into the database; all data has been questioned answered and entered into the database table; all case report forms has been the main researchers signature ratification; non-case report form data (for example, the central laboratory of electronic data) have been merged into the test database, and complete database with test data consistency verification; medical coding has been completed; the completed final logical data and consistency of verification results of the review; has completed the final review of manifest error or anomaly; have completed final medical verification; data quality audit has been completed, the error rate and quality audit found recorded in the document; according to SOP update and save all the trial-related documents.

Once you have completed the above steps, it should be approved in writing by database locking,

test personnel by signature and date of signature, test personnel include: data management, biostatistics division, CRA representatives, researchers and representatives. Once the database locking written approval documents, it should recover the data editing permissions to the database and recover the data recorded on the date permission to edit the document.

For interim analysis, should be strictly in accordance with the program specified time points or event points for analysis, database locking interim analysis process and the final analysis, database locking requirements may vary, but all the requirements of database locks and the steps taken should be recorded in the file in the case should also be reported to the data as of the time of interim analysis, the situation and end time events and so on.

2. After the database is locked data error

If database locking find data errors, careful consideration should handle these errors and record data. Most importantly, we should assess the potential impact of these errors on the data analysis and the effectiveness of the safety analysis. However, not all the data found errors must be

corrected database itself. Data error may be recorded in the statistical analysis of clinical reports and documents. Although some sponsors choose to change all the errors found in the database, but some sponsor may only change the safety / have important implications for the effectiveness analysis of data errors. Most importantly, the sponsor should determine in advance a program to determine which data should handle errors and record these data errors.

If a database lock and then unlock again, this process must be carefully controlled, carefully documented. Re-unlock the database notification process should include the project team, which clearly define the change data errors, change the date and reason for the change, and signed by the principal investigator, data management and statistical analysts and other personnel. Database locked again and should follow the same notification database first locking / approval process.

(Xii) data backup and recovery

Throughout the study of data management process, you should back up the database in a timely manner. Usually backed up on a separate stand-alone computer, and the weekly backup files

synchronized according to the progress of work. Final data set will be in the form of CD-ROM backup, if necessary, the data set is not locked disc can also be backed up.

When the database irreparable damage, the database should be used to restore the most recent backup, and added the corresponding data entry.

Related computer must have appropriate and effective anti-virus settings, including firewall, virus scanner and the like.

(Xiii) Data Retention

The purpose is to ensure the preservation of data security, integrity and availability of data (Accessibility).

Ensure data security is to prevent data may be subjected to physical damage or destruction. The process of conducting clinical trials, all the collected raw data (such as CRF and electronic data) is stored in a safe place, such as a controlled room to ensure the appropriate temperature, humidity, it has a complete fire safety measures, fire lockable document cabinet. The original document is part of the audit trail to track the raw data should be made as an electronic audit trail to record any modification or backup of the database as strict protection. Data

retention requirements should be performed in accordance with specific regulations.

Time content and data be entered into the database, and data entry in the database history of all changes require intact. Ensure data availability means that the user can freely when needed login and access to data, and data in the database can be transmitted promptly as needed.

After the completion of clinical trials, coping during the test document archive. The following table summarizes the clinical trial data filed with various types of information:

Archived Content	Claim
Clinical trial data	All test data collected. These data include both data recorded on the case report form also includes data collected in a non-case report forms (such as laboratory results, ECG results, and the subject electronic diary).
External Data	External collected and introduced into clinical trial data management system (the CDMS) data, including all imported data and files for all files and external data quality control.
Database metadata information	Clinical trial data structure information. Such information is a typical table , variable names, forms, visits, and any other related objects, including a list of coding.
Data Management Plan Book	Microsoft Word data management plans , or PowerPoint document can be converted to PDF format or printed to paper files archived.
Coding dictionary	If the data is provided with a company or synonyms dictionary tables are automatically encoded, dictionaries and unified vocabulary used should be archived.
Laboratory reference range	Laboratory reference range. If the pilot clinical study using multiple versions of the reference range, the reference range for each version should be archived.
Track Inspection	Test entire contents of the inspection track, and use of anti-modified manner.

Logic test, derived data change control list	Provide logical test definitions and derived data to worklist, working document, in the form of the work report of the algorithm, as well as their change control records.
Data questioning Table	All data related messages questioned table, data transfer and data table question question answer sheet copy. Paper forms of data can be questioned table scans archived and add an index to scan files.
code	Data quality verification procedure code, the code and the data derived from the statistical analysis of clinical trial data code. Code documentation should be archived. The ideal situation is that these files are stored in online mode, and Index or hyperlink.
Case Report Form PDF image File format	Case report forms for clinical trials for the paper, CRF image file can usually be obtained by scanning, and these scans files into PDF format. For clinical trial electronic data collection, the electronic forms PDF format image files by EDC / M applications created.
other	Other data management-related documents, such as database locking and unlocking library records, database user lists.

The following table illustrates the different types of clinical trial data and common archive format.

format	description
CSV	Comma-delimited ASCII text file, you can use a text editor, word processor and Excel spreadsheet editing software.
XML	In ASCII technology, ease of conversion between different systems of structured information.
XPT	SAS source file format provided. Typically used to submit data from clinical trials.
Adobe PDF	Widely used text output format.

Clinical trials for the use of paper-based case report form, Institutions should maintain copies of all paper-based case report form. For the test the use of electronic data, clinical trial data management system vendor shall provide a copy of all electronic case report form for the clinical research

organization PDF file format to record.

(Xiv) the subject of data confidentiality and protection of personal privacy

1. Data Privacy

Data privacy is a fundamental principle of the drug development process must be followed, agencies involved in drug development should establish appropriate procedures to ensure the confidentiality of the database, including the establishment and sign a confidentiality agreement in order to regulate the behavior of the appropriate personnel, and the establishment of a security system to prevent the database leaks.

2. The subject of the protection of personal privacy

Clinical trial of privacy should be fully protected, protected health information includes: name, date of birth, unit, address; ID card / driver's license and other identification number; telephone number, fax, e-mail; health insurance number, medical records the account; biometrics (fingerprints, retina, sound, etc.); photographs; hobbies, beliefs and so on.

Protection of privacy in the design of the database should be considered at the technical level, and do not affect the integrity of the data does not violate the GCP conditions do not include the

above principles as protected health information, such as: database should not include subjects full name, and should refer to specific code.

Sixth, security and data quality assessment

Objectivity and reliability of the quality of clinical trial data not only directly affect the test results, but also related to the study and the conclusions the entire clinical research. Establish and implement quality assurance and assessment measures to ensure the quality of clinical trial data is critical.

(A) Quality Assurance

Quality Assurance need to determine the organization, specifically in data management staff should have the qualification requirements, responsibilities, and permissions; quality assurance must possess the necessary resources, including personnel, equipment, facilities, funds, technologies and methods; to ensure the organization predetermined requirements, SOP 's development is very important , because SOP is the behavior of the data management work norms and guidelines, which specify the work by the department, team or

individual to do, what to do, what method to use to do what under ambient conditions and so do; there should be a quality assurance mechanism to ensure that it is complied with, the staff does not perform to give a warning when specification or operating out of control, internal quality audits and inspection, are common mechanism to ensure continuous quality improvement.

Quality assurance and quality control improved from (at Quality Control, the QC), quality assurance (at Quality Assurance, the QA) and CAPA (Corrective and Preventive the Action the Action, the CAPA) and other activities.

1. Quality Control

ICH E6 quality control will be defined as " operating techniques and activities within the quality assurance system are taken to verify the clinical trial-related activities are in line with quality requirements. "

Clinical trial data quality control applied to every aspect of data processing, such as clinical research organization, data audits, process management computer system life cycle processes and data.

(1) clinical research organization and quality control

All clinical researchers should be qualified and trained. Development of quality control procedures, such as:

Security: clinical researchers have been trained, and in accordance with rights management procedures;

Equipment: clinical research personnel in accordance with procedures to ensure safe and appropriate equipment and data storage;

Subjects Privacy: Make sure to follow the procedure to protect the privacy of the subject;

Quality Audit: clinical researchers data internal audit;

Storage and archiving: ensure that the data files are stored and archived.

(2) Audit and Quality Control

Clinical data quality control audit is most commonly considered aspects, including:

CRF data review;

Electronic Data integrity: to ensure that electronic data is full, complete and accurate;

Programmed Data Verification: Confirm compliance program, the subject security;

Traceability;

Original Data Audit: confirm the original file intact to detect unreported data (eg adverse events);

Appropriate use of computer systems: recognize staff be trained to use rights management, and can properly use the computer system to complete assigned tasks.

(3 Lifecycle) process computer systems and quality control

Such as the use of computer systems, test and shall be allowed to meet the needs of staff. Each step in the life cycle of the system are required to perform quality control to ensure that all requirements have been recorded and tested to meet. E.g:

Requirements: Ensure operation and maintenance of the system covering all users as well as technical, commercial and regulatory requirements.

System validation process: Make sure to follow the procedure established system to verify and

record complete and accurate.

Change control: the life cycle of the system during all changes are subject to evaluation and testing.

(4) data management processes and quality control

Usually from CRF design start, ensure the quality of all data management, factors to be considered include: the design proper, and other compliance programs, data collection environment and training; quality control checks, for example: data entry system; data valid range verification; logic verification; security check.

Data management, two different working nature of the data administrator's decision two quality control: process quality control (in the QC-Process) and real-time online quality control (ON-Line the QC).

For the design of quality control, such as CRF design, logic design, and the establishment of a database of test, more commonly used process quality control methods, quality control process can ensure the quality of each stage of the design

process is reliable. For example, quality control inspection logic is entered through a different test data to check if the logic test a computer program can properly capture the " problem " of data. If not, then the logic test need to be modified and tested again until the correct date.

Clinical trials for quality control stages, and more generally the use of real-time online quality control. Real-time online quality control is to calculate the error rate of a point in time data to assess the quality of the data. For example, real-time online quality control report showed 3 subjects have completed the entire trial as planned, but the subject of a visit of the laboratory data entry yet. At this point the data quality control requires the administrator to find the problem and timely mechanism to start questioning.

2. Quality Assurance

ICH E6 of the quality assurance is defined as: " To ensure the test conducted and data are generated, on file (recording) and the report are in line with the GCP . All planned and applicable regulatory requirements established behavior into

the system ."

Most of the sponsor or CRO and others have independent data quality assurance department, whose main task is to establish quality management system, namely the development of quality policy, quality manual and plan, the SOP and so on, to assess whether the data management process requirements, whether the program execution, and audit data quality.

(1) Standard Operating Procedures (the SOP)

SOP is a detailed written instructions to achieve uniformity, to complete a specific mandate enacted. Formulate SOP significance is possible to control a variety of primary, objective factors on the clinical trial results, and minimize error or bias in clinical trials, and to ensure true and reliable research data to improve the quality of clinical test results.

In general, data management SOP may include the following: Data Management Plan; CRF design; CRF fill Guide; establishing a logical examination;; the establishment and design of the database CRF tracking; data entry; data verification and clean-up; external electronic data management; medical coding; the SAE consistency verification; quality

control database; locking and unlocking the database; preservation and archival data; data security; CRO selection and management; personnel training.

SOP establishment should be able to cover all the data management process, but the important thing is established SOP compliance. SOP formulation will not step the need to continuously improve and develop in practice.

(2) inspection

The sponsor shall also establish inspection departments, quality system compliance systematic inspection by personnel not directly involved in the test on a regular basis to determine whether the recording of test execution, data analysis and reporting whether the test program has been approved, the SOP , and GCP consistent understanding of misunderstanding or error causes and propose preventive and corrective recommendations. Data management requires inspectors to check not only experienced inspectors, and to be familiar with the process of data management and the corresponding computer program, in particular, be familiar with the clinical trial data for regulatory standards and requirements.

Data quality management audit is a systematic review of the entire data management, which consists of three layers: a meet the regulatory requirements of data management SOP ; shall provide written documentation of SOP compliance (eg compliance database locking SOP process generated when the recording) ; based on the above, there are other objective evidence to support the data processing to produce reliable high-quality data, can be used for statistical analysis and reporting, etc.

For the inspection of clinical trial data, the general concern of four parts: research files, data, statistical data analysis, clinical study report.

File and data management related to the audit are: curriculum vitae and training records data manager, data management of the job description and requirements, data management plan, receiving CRF change records, data verification and clean-up of the list of records, database records control , change control recording logic test and the like.

The main contents include data auditing: of CRF consistent with the source data, of CRF completeness and consistency of data in the database, data management processes and

compliance data and the like.

(3) corrective and preventive action (the CAPA) system

Root cause analysis and corrective and preventive action is the basis of the quality of the system, the CAPA is the core of continuous quality improvement.

Corrective measures are already against the existence of the phenomenon does not meet or undesirable, to eliminate the root causes of its measures taken to prevent the repetition (the Recurrence). Preventive measures are for potential nonconformity or potential undesirable phenomenon, measures to eliminate the reasons taken to prevent (Occurrence).

A deep understanding of data management systems and data management processes to the establishment of an effective CAPA system, thereby strengthening the quality management system to ensure that the purpose of all production data management processes are in line with clinical trials, as well as to ensure the safety of participants and data integrity sex. Measure CAPA a system or a process within the system meets the test object requires a thorough understanding of data related to

the management of inputs, outputs, controls and resources. The validity and effectiveness of a clinical trial to assess the quality management system, including the definition and evaluation of the measures related to feedback.

(B) quality assessment

True, accurate, complete and reliable basic principle is to ensure that the clinical trial data quality. Good data quality should meet the following requirements:

ALCOA : attributable sex (attributable) , legibility (legible) , simultaneity (contemporaneous) , Original (Original) , accuracy (Accurate) .

+ ALCOA : Integrity (Complete) , consistency (Consistent) , persistence (Enduring) , availability (the Available the When Needed).

Assess data quality indicators may include: time data entry and reporting; auditors or inspectors to confirm the number of observations in question, or the number of correction; the time required to resolve the issue that; of CRF review times; data error quantity.

Erroneous data collected in clinical trials must be as small as possible, so that it can support the conclusion that the clinical trial found or obtained. By

finding clinical trial data transcription errors, transfer and processing of quantitative data quality and assess its impact on the correctness of the results of clinical trials are necessary.

Found that the main method of data verification confirmed the wrong active, logic testing, data verification, summary statistics, of CRF and database checking and so on.

The most commonly used method to assess the quality of data is to calculate the incidence of erroneous data, the error rate. Data entry errors sum / = checked error rate found.

For CRF key indicators for verification, the database will be 100% of the review, and CRF and doubt reconciliation table, all errors discovered are corrected. For the verification of non-critical indicators, if the total number of cases is greater than 100 , it will be randomly selected 10% of the cases for review; if less than 100 cases, the number of cases to extract the square root of the total number of cases for review. The database with CRF and questions table check, acceptable error rate: variable value does not exceed 0.2% ; text tag does not exceed 0.5% . If the error rate exceeds this standard will be 100% checked.

Key indicators to define non-critical indicators by the investigator, sponsor and statisticians to discuss the decision.

7, security of data and reporting of serious adverse events

A key objective of the clinical trial is to identify, study, establish or showed samples of a study on the safety features of the product. Test management and reporting of safety data should support this purpose. In the management and reporting of clinical trial data, the security of the data is often the most challenging.

Many research institutions to establish a data security and audit committee (the Data and the Safety Monitoring Board , the DSMB), clinical trial safety data for verification. The committee of independent research in the implementation of the medium-term analysis and data verification personnel, can blinding may not blinding. Study pause being implemented by the data monitoring committee following reasons make recommendations or decisions :(1) a very significant effect; (2) an unacceptable security risk; (3) invalid. The committee can also recommend the study of changes being implemented, for example, lower

dose, study groups appear to remove an unacceptable security risk.

Medical inspectors sponsor of safety data should also be checked.

(A) adverse events capture, management and reporting

Clinical studies of safety data is not only a rich source of information, while its management and reporting is also the most challenging. Clinical adverse events in clinical studies of the most important security information is often contained. In order to ensure the collection, coding, analysis and reporting methods useful for obtaining reliable conclusions, we need to understand the characteristics and limitations of adverse event data. ICH provides some guidelines for the industry on how to manage and report clinical trial data security guidelines, such as ElA , the E2A , E2B , E2C , the E3 , E5 , E6 and E9 .

When the security of the data acquisition, managing, and reporting: design CRF need to collect safety data give sufficient attention; to define the severity and understand the uses and limitations; ensure the normal range correctly and laboratory

data association, at different research institutions laboratory data were aggregated to note the normal range is the same; the analysis and reporting of laboratory data, change of category (from a normal state into an exception) and the magnitude of the change are to be considered ; analysis of adverse event data accuracy and data acquisition and reporting methods related.

In clinical trials, adverse events should be in accordance with the standard dictionary or glossary classified and coded. Dictionary is selected to meet the purpose of the study, it is best representative, in accordance with industry standards. Dictionary installation, maintenance and upgrades to a set of standard operating procedures. Upgrading should be evaluated prior to the dictionary upgrade on existing clinical trial data encoding, and proposed solutions. Select the appropriate coding method and coding program. Coders have a certain clinical knowledge and access to appropriate training. Encoded data required for quality control checks.

It can be applied in many ways the security of the data display and reporting. In order to ensure

adequate results belong drug reaction reporting, and the need to determine the scientific selection, data to identify trends and salient features. Drug reaction was carried out to identify the purpose of security is the driving data processing and reporting.

(B) laboratory data

Characteristics of laboratory data needs to be considered in the data management. Data storage unit should be able to clearly reflect the value of the data; in many databases, and data units are separate. One aspect of the management of laboratory data is the most challenging connected data to the appropriate normal range. In obtaining the data, if the data is not the data administrator arrives electronically, where data and connections its proper normal range will cost a lot of energy. When the normal range can not be obtained, you can use the reference range, which is obtained from the range of the normal range of derivatives, or can be obtained from reference books from the study. However, instead of using the normal reference documentation for database users must be clear.

For easy data connection between studies,

often using standardized technology laboratory data, in order to achieve this purpose. Standardization generally include, when the value is normal, the data into unit-value of "0" and "1" , when the value is below the lower limit of the normal range, the value is converted to less than "0" , when the value is higher than upper limit of the normal range, the value is converted to greater than "1" . Laboratory quality control itself should reach the country or region specified.

(C) Other data

In addition to adverse events (AEs outside) and laboratory values, safety and other forms of data. Specific test data (such as ECG, EEG) data collection and the need for a common format, precision, and special attributes from these tests have to understand.

Physical examination in clinical trials are very common. Broadly speaking, physical examination is a screening method; if a unexpected, clinically significant abnormalities were found in physical examination to determine the use of this special event is usually detected. In this case, the data

obtained from the special detection with greater reliability.

It does not encourage the use of open-text description of the data. Of " other data " management trust in the form of information. For the physical examination and special inspection, free text comments are allowed. Text boxes can be computerized by word processing rather than data entry system, to connect with the database, but not as part of the database itself. At this time correction mode is proofreading, instead of double entry. Some sponsor in order to avoid the lengthy text notes computerized, and the use of coding methods, such as "0 = no comment " , 1 = " notes, irrelevant " , 2 = " notes, the relevant " , 3 = " There Note, the key " .

(Iv) serious adverse event data

Clinical research, regulatory requirements for timely reporting of serious adverse events (SAEs). Some companies usually set panel processing and reporting SAEs , at this time of the report content, format and timing requirements and CRF fill may not be exactly the same, these security and data reporting is generally complete in pharmacovigilance

database, the database typically includes various different sources of safety data may be incomplete, repetitive, fragmented, or inaccurate. The clinical trials database based CRF fill SAEs is to undergo a rigorous process of data management procedures, including clean-up, questioning and verification to ensure accuracy. Two databases SAEs may differ records to ensure SAEs data consistency must be consistent with the pharmacovigilance database of clinical trials database for verification. The verification must be carried out regularly in clinical trials.

The scope of verification may include but is not limited to the following: program; researchers; the subject code (random number); subjects initials, date of birth, gender, race; number of cases of serious adverse events; adverse event diagnosis; report serious adverse event name; coding terminology or preferred term; adverse event start date , end date; the date of death, cause of death and autopsy results; adverse event outcomes; adverse event severity; due to adverse events for measures of medication taken, concomitant

medications start and stop using the name and date; sponsor and the investigator to assess adverse events, evaluate the content should include: severity, causality, whether expected or without unblinding. Assessment of adverse events need to use the standard dictionary coding terminology; adverse events are reported to the authorities, when to report.

VIII Glossary

Verification system (the System the Validation): refers to establishing documented evidence computerized system life cycle management to ensure the development of computerized systems, implementation, operation and maintenance and other sectors are able to consistently meet its preset height of various systems of technical standards , purpose and quality attributes, and in the monitoring of quality control procedures, and can be highly reproducible and can maintain the standards and functions of the system put in its application until the decommissioning process in line with regulatory requirements.

Track inspection (Audit Trail): is a computer

system (such as the Data Management System) basic functions. It refers to a system using electronic record mark with a time of security and computer-generated, so that the user can independently traceability system input, modify, or delete the date, time, and every reason to modify the electronic data record for future reproduction data. Will not change any records of past records are concealed or disappear. As long as the subjects of electronic records preservation unchanged.

Access control (the Access Control): refers to the identity of a user identity in accordance with the clinical testing of electronic systems and the definition of an ownership group to allow, restrict or prohibit the access or use of the system, or system of an information resource items access, enter, modify, view technical ability to control.

External Data (External the Data): Data is provided by the external data acquisition side. Transfer external data can be uploaded via electronic data or direct docking way to clinical data management system, through the integration of data and then analyzed; or may not be integrated with the

clinical data in the database, the data analysis, as a separate data source, and clinical data within a database together directly involved in the data analysis. External data includes multiple data sources, the majority of electronic data package upload, non-paper records or entered directly into the EDC data systems.

Electronic Signatures (Electronic's the Signature): refers to any form of electronic documents means (such as a symbol or series of symbols composed dataset) contained in or attached to identify the signer's signature. This is performed by an individual, use or authorize the use of its electronic signature handwritten signature has the same legal effect. In clinical trials, experimental data and files on any electronic signature indicates that the electronic signature has accepted or recognized by the relevant electronic records or data file contents, symbols, or program it has signed.

Data Management Plan (the Data Management Plan, the DMP): is a dynamic document by the data management program based on clinical trials of writing, it is detailed and comprehensive regulations

and record data management tasks for a particular clinical trial, including personnel roles, work content, practices and so on. DMP revised and upgraded accompanied throughout the trial stage.

Electronic data capture (Electronic's the Data Capture, the EDC) : is based on technology used in clinical trials data acquisition computer network, software, hardware, the SOP combine and staffing to electronic form of direct collection and transmission of clinical data.

Logic verification (the Edit Sprawdź): refers to the examination of clinical trial data entered into the computer system for data validity. Such verification can program logic, subroutines and mathematical equations system and other methods to achieve, the main evaluation of data input fields to its expected value logic, value range or numeric attributes, etc. for errors.

Blind review (Blind Review,): refers to the end of the experiment (the last subject last observation) to collate and evaluate before unblinding the data in order to finalize the statistical analysis plan.

Database lock (Database Lock): data

management based on the data management plan (the DMP) Close clinical trials database, so that can not be changed. It is in clinical trials end, the EDC system, all doubts were resolved, after the approval of the relevant procedures for implementation. Locked databases generally can not be changed.

Source data verification to confirm (the Source the Data the Verification , SDV): refers to the evaluation of clinical trials recorded in the case report form data and source data consistency of conduct to ensure the integrity of the data collection, accuracy and reliability, making the clinical pilot projects in the future to reproduce possible.

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