appendix

药物临床试验期间安全性数据快速报告常见问答（2.0 版）

I. Introduction

To further promote ICH "E2A: Management of clinical safety data: rapid Reporting Definitions and Standards" E2B(R3): Management of Clinical Safety Data: Individual Data Elements Transmitted in Case Safety Reports" "E2B(R3) Area of Case Safety Reports" Implementation Guidelines for Regional Implementation to promote safety data during drug clinical trials Rapid reporting standards are unified to improve data quality. The National Medical Products Administration The Center for Drug Evaluation (hereinafter referred to as the Center for Drug Evaluation) is based on the latest work requirements and recent years. to quickly report existing problems, classify and summarize each problem, and proceed one by one After discussion and confirmation, the "Safety Data During Drug Clinical Trials" was systematically sorted out. Updated and improved according to the Rapid Reporting Frequently Asked Questions (Version 1.0) to form a new version Frequently Asked Questions and Answers for Applicants and Contract Research Organizations (Contract Research Organization, CRO) Reference.

This Q&A is based on current knowledge and will be continuously added or updated in the future. exist During reference use, please pay attention to refer to the latest version.

2. Questions and answers about the scope of rapid reporting

1. "Standards and Procedures for Rapid Reporting of Safety Data During Drug Clinical Trials" (hereinafter referred to as the "Standards and Procedures") refers to the applicant's approval to carry out drug (including (including traditional Chinese medicine, chemical drugs and biological products) after clinical trials, during the clinical trials

Suspected and unexpected serious adverse reactions to experimental drugs (Suspected

Unexpected Serious Adverse Reaction, SUSAR) and other potential

Information about serious security risks should be reported promptly. Drug and clinical trial scope

What does it include? Are vaccines included?

Answer: Drugs include traditional Chinese medicines, chemical drugs, and biological products related to registration applications.

Vaccines are biological products. Therefore, vaccines must also be produced in accordance with the "Standards and Procedures"

Run a quick report. Clinical trials include phases I, II, and III related to registration applications.

Clinical trials and other approved clinical trials (such as increasing indications, etc.)

clinical trial application), bioequivalence (BE) test, attached

Conditionally approved drugs need to complete the required clinical trials and marketing authorization documents

Phase IV clinical trials with special requirements.

SUSAR obtained by the applicant from other sources during the above clinical trials

and other potentially serious security risk information should be reported quickly.

2. What do the above “other sources” usually include?

Answer: Other sources generally refer to clinical trials of the same drug at home and abroad,

Spontaneous reports, animal or in vitro experiments and others (e.g. literature, regulatory agencies,

publications) etc.

Spontaneous reports from domestic and overseas sources, which are not observed in clinical trials

Suspected adverse reactions do not need to be reported in accordance with the rapid reporting requirements. Dan Shen

Petitioners should review reports from all sources and regularly evaluate accumulated data to update security

Complete information and identify new safety signals, and report to the Center for Drug Evaluation when necessary.

3ÿ What does "other potentially serious security risk information" refer to? by application

What are the requirements for the time limit and content format of the application window report?

Answer: Generally speaking, for information that significantly affects the risk-benefit assessment of a drug or information that may consider changes in drug usage or affect the overall drug development process, All can be classified as "other potentially serious security risk information", for example: (1) For known and serious adverse reactions, the incidence of which is increased and judged to be of serious significance Must have clinical significance; (2) There is obvious harm to the exposed population, such as in the treatment of dangerous Drugs lack efficacy in life-threatening diseases; (3) In recently completed animal experiments, there are Significant safety findings (e.g. carcinogenicity).

In the above situation, the information that needs to be reported quickly is not a case report, but It needs to be submitted 15 days after the applicant determines that it is other potentially serious security risk information. Make a quick report within. There are no mandatory requirements for the content format of the report. Subject to information reported. Generally address other potentially serious security risks and risk control measures taken, and provide relevant information.

4. How to judge the predictability of adverse reactions?

Answer: Unexpected adverse reactions refer to the nature, severity, and consequences of the adverse reactions. result or frequency, which is different from the current relevant information on the investigational drug (such as the investigator's manual, etc. documents). The researcher's manual is often used as a guide to determine whether a bad The main reference document for whether the response is expected, please refer to the "Investigator's Manual" for details. Technical Guidelines for Writing Security Reference Information.

5. Obtain clinical trial approval before May 1, 2018, but have not yet Should clinical trials be completed in accordance with the "Standards and Procedures"?

A: As of May 1, 2018, ongoing clinical trials or trials

Shixin's clinical trials are all conducted in accordance with the "Standards and Procedures".

6. Different uses of the same drug carried out overseas (such as drug dosage, dosage form,

route of administration) or use (such as indications or applicable populations)

Need a quick report?

Answer: Reporting is required. If the usage or purpose of a drug appears to be consistent with the rapid

Adverse reactions should be reported promptly and it is recommended that interactions with other uses or uses of the drug be

Report reference. This may result in some degree of over-reporting or unnecessary reporting

(e.g. reporting phlebitis with intravenous administration to countries where only oral dosage forms are used),

But it can avoid false negatives.

7. The causal relationship is "possibly irrelevant", "cannot be evaluated" and "to be evaluated"

Do cases need to be reported quickly?

A: Assessment of causal relationships is critical for rapid reporting. for

All adverse events reported by investigators or applicants, if judged to be related to the trial

Any possible cause-and-effect relationship with a drug can be considered an adverse drug reaction.

As the responsible entity, the applicant should carefully evaluate the researcher's assessment as "possibly unavailable".

If there is reasonable evidence to support the existence of a possible causal relationship,

Rapid reporting is required as required.

"Unable to evaluate" and "to be evaluated" statements identify new safety issues at an early stage

The question is of no value if the researcher cannot determine the relationship between the adverse event and the experimental drug.

Relevance, applicants should communicate with researchers and encourage them to assess relevance.

If the causal relationship judgments of both the researcher and the applicant are "unable to evaluate" and "pending evaluation"

"Value", further clarification should be made as to whether there is a possible causal relationship before deciding whether

Need to report quickly.

8. The experimental drug is a compound preparation, in which a single active ingredient is

How is safety information obtained from other sources reported?

Answer: If a single active ingredient is obtained from other sources, it belongs to other categories.

Potentially serious safety risk information needs to be reported quickly.

9. When reporting on individual cases, is it possible to remain blind without clarifying the use of

Is the test drug, active control drug, or placebo used?

Answer: When serious adverse events occur, causality evaluation should be carried out, which is

SUSAR is required to report expeditiously in accordance with the Standards and Procedures.

When an unexpected serious adverse event occurs in a blind trial, the applicant may only

Emergency unblinding is performed on a case-by-case basis. During this process, only individual specialized personnel carry out individual

The case was urgently unblinded, while those who analyzed the efficacy results and conducted clinical trials were still

Blinding should be maintained. Through reasonable clinical trial design and management, individual cases can be urgently revealed

Blinding generally does not affect the conduct of the clinical trial or the analysis of the final results.

If blindness is maintained without emergency unblinding of individual cases, the trial cannot be clarified in a timely manner

Drug, control drug or placebo will not be conducive to risk control in drug clinical trials.

Regulation and subject protection. Therefore, urgent unblinding of individual cases is required, which is consistent with rapid

Only those reporting standards can make case reports as required.

10ÿ How to report serious adverse reactions occurring in the positive control drug group?

Answer: If serious adverse reactions occur in the positive control drug group, the drug manufacturer should be informed.

Municipal license holders and/or clinical trial institutions submit to the National Center for Drug Evaluation

Report.

11. Do serious adverse events in the placebo group require rapid reporting?

Answer: Serious adverse events in the placebo group do not require rapid reporting of individual cases.

Information related to other potentially serious security risks needs to be reported quickly.

3. Questions and answers about the time limit for rapid reporting

12. For fatal or life-threatening SUSAR, the applicant should first obtain

Report as soon as possible after being informed, but no later than 7 days, and report within the next 8 days,

Improve follow-up information. Does the subsequent 8 days refer to the 8 days after the first report or the first

Within 15 days after the report is received? What is the time limit for receiving the follow-up report later?

Answer: For fatal or life-threatening SUSAR, the applicant should

Report as soon as possible after being informed, but no later than 7 days, and 8 days after the initial report.

Submit a follow-up report with as complete information as possible within the day.

Subsequently, new information will be submitted in the form of a follow-up report or the previous report will be updated.

When changing information, the reporting time limit is 15 days from the date new information is obtained.

13. For international multicenter clinical trials, when does rapid reporting begin?

When will it end?

Answer: Starting from the domestic clinical trial approval date/implied license date,

until the marketing authorization for the drug is obtained within the period or until it no longer continues research and development in the country.

14. For conditionally approved drugs, clinical trials and listings must be completed as required.

For phase IV clinical trials with special requirements in the municipal license approval document, when will the rapid report start?

When does it start and end?

Answer: Starting from the first subject in the country signing the informed consent form, to the latest trial in the country

The follow-up of the latter subject ended.

15ÿ When submitting a report as an XML file through the Applicant Window, is it also

Will the Acknowledge character (ACK) be returned? How about 7/15

The time limit of the day is defined?

Answer: When submitting a report as an XML file through the applicant window, you can return

Return ACK. Applicants should check the contents of the returned ACK in a timely manner.

If the upload fails due to its own problems, it should be corrected in time so that the report can be successfully imported.

The date of uploading of the report shall prevail.

4. Questions and answers about the rapid reporting method

16. There are currently two transmission methods for case reports (Gateway method and application

Is the method of uploading XML files through the window) an option? Is it possible to stop halfway?

Change submission method?

Answer: Applicants can choose any of the above transmission methods by themselves;

Change submission method. It is recommended to transmit via Gateway.

17. The company has not established a pharmacovigilance system. Can it be carried out through other means?

Case reports, such as submission of CIOMS form by mail/paper/other means?

Answer: Currently, the case report transmission method is limited to Gateway method and application.

XML files can be uploaded via Renzhuang. Submissions via email/paper/other methods are not accepted.

Submit CIOMS form, etc.

For those who have not yet established a pharmacovigilance system and cannot pass the Gateway method and

Applicants who submit case reports by uploading XML files in the applicant window can

To entrust a third party (such as CRO) to perform reporting.

18. Occurring after the clinical trial is completed and before the approval conclusion is obtained

SUSAR and other potentially serious security risks, what channels should applicants take?

Report it? Is it consistent with rapid reporting before the end of the trial?

A: Consistent with rapid reporting before the end of the trial.

19. What about SUSAR that uses drugs in clinical trials as "combination drugs"?

Report it?

Answer: Drugs approved for drug clinical trials are planned to be combined with other drugs.

For combined use of drugs, the applicant shall submit a new drug clinical trial application, and upon approval

Clinical trials of new drugs can then be carried out. If the combination of drugs is not on the market, it is recommended that

It is up to each applicant to negotiate and confirm that one party is responsible for reporting so that SUSAR does not repeat

Repeated reporting and underreporting. If unmarketed drugs are combined with marketed drugs (increased indications

or functional indications, etc. that require application for new drug clinical trials),

SUSAR occurring in unmarketed drugs is reported to the Center for Drug Evaluation and is only related to marketed drugs.

drug-related serious adverse reactions, the drug marketing authorization holder and/or clinical

Clinical testing institutions report to the National Center for Drug Evaluation.

20. After the initial report, a follow-up report found that the case did not fall under SUSAR or

How should I report if the information reported for the first time is incorrect? Need to cancel?

Answer: No need to revoke. After the first report, if the case is found to have declined during follow-up

The level is non-SUSAR and should be included in H.1 (Case Narrative Including) of the follow-up report.

Clinical Course, Therapeutic Measures Outcome and Additional

Relevant Information) field indicates the reason and basis for downgrade; if during follow-up

If the reported information is found to be incorrect during the follow-up report, it should be coded in the follow-up report and filled in in accordance with the

In the field of E2B(R3) business rules, for example, select "Nullification/Amendment" in the C.1.11.1 (Report Nullification/

Amendment) field.

"Amendment", and explain the situation in the H.1 field, such as reporting

Report information errors, etc.

twenty one. Applicants should complete system configuration in a timely manner and follow regional implementation guidelines

Implementation of E2B(R3) is required no later than July 1, 2022. Then this

Do case reports previously reported in R2 format need to be submitted in R3 format?

Answer: No supplementary report is required. From July 1, 2022, only eligible areas will be accepted

Implementation of case reports required by the guidance.

twenty two. E2B (R3) data element Gk2.2 (Medicinal Product Name as

If multiple drugs are involved in Reported by the Primary Source), how should they be arranged?

Column order?

Answer: In order to facilitate unified management, the suspected experimental drug should be filled in first.

The drug name must be filled in with the name of the experimental drug when it applied for IND in China.

The remaining drugs are arranged in descending order of suspicion.

twenty three. How should I fill in the acceptance number in the case report?

Answer: Phase I, II, III clinical trials and other approved clinical trials

For verification, fill in the IND acceptance number or supplement the application acceptance number. BE test filling acceptance

number or registration number. Conditionally approved drugs need to complete the required clinical trials and

For phase IV clinical trials with special requirements in the municipal license approval document, filling in the marketing application is subject to

Reason number.

Individual case reports from within and outside China must be registered with GkCN.4 approval number/license

Enter all acceptance numbers obtained for the drug in the country under the acceptable number. If applicable, will

The clinical trial acceptance number to which this case belongs is listed first.

twenty four. Is it possible to have multiple acceptance numbers for the drug involved in the same clinical trial?

Only submit a case report once?

Answer: The same clinical trial involves multiple acceptance numbers for the drug (such as a Phase I

Clinical trials involve multiple specifications of experimental drugs, etc.), and only one case report is submitted.

And list all acceptance numbers of the drug under GkCN.4.

25. According to the E2B (R3) regional guidelines, the acceptance number should be filled in the data

Under the element GkCN.4. If there are too many acceptance numbers involved, the number of characters under this item

Unsatisfied, how to deal with it?

Answer: If the number of characters under GkCN.4 cannot be met, you can fill in the data

Under element H.1.

5. Questions and answers about rapid reporting entities, account management and testing issues

26. If the applicant plans to entrust a third party (such as a CRO) to assist in submitting a case

Report, how to identify the reporting subject?

Answer: The applicant signed a service contract with the CRO company, but as a drug

R&D and registration sponsor, the applicant is still responsible for safety supervision during clinical trials

and the person responsible for the report. Whether using the Gateway method or the applicant window

When uploading an XML file, the enterprise identification ID must be the applicant's identification ID.

27ÿ The "ICSR Electronic Transmission Account Application Form" requires filling in the "Electronic Transmission Account Application Form"

"Identification ID of the enterprise in the transmitted information". Is there a standard for the preparation of identification ID?

Answer: The enterprise identification ID is defined by the applicant and there are no strict preparation rules.

Fan, you can use the English name or abbreviation of the unit name, Chinese pinyin or abbreviation, etc.

Punctuation/special characters are not recommended.

28. The applicant is a foreign company and currently does not have an entity or office in China

There is no unified social credit code for enterprises. How to apply for an applicant window account?

Number?

Answer: The number of foreign companies involved in this situation is small and the situation is relatively special.

Currently, you can entrust a CRO/domestic agent and use its applicant window account

Quickly upload an XML file through the Gateway method or the applicant window.

Report.

29ÿ The company registration department already has an applicant window account and would like to apply again.

Is it feasible to have an account dedicated to quick reporting?

Answer: According to the current applicant window account registration management regulations, a legal person

An entity can only register one main account in the Applicant Window; different accounts can be set up under the main account.

sub-accounts to meet the needs of different departments or different affairs within the same company.

30. Is it necessary to test in advance before making a case report?

Answer: No matter you choose the Gateway method or the applicant window to upload XML

For individual case reports in the form of documents, applicants must first submit a test report.

A formal report will be submitted after approval.

31. When testing with the pharmacovigilance system of the Center for Drug Evaluation, different drugs

Do drugs, test protocols, or switching to different pharmacovigilance systems need to be tested separately?

Answer: If the applicant uses the same pharmacovigilance system and identification ID, it will be different

There is no need to test the drugs and trial protocols separately; if the agency applies for different

If the human agent reports, that is, if the identification ID is different, they need to be tested separately.

If the pharmacovigilance system is changed during the reporting process, it is recommended to contact the Center for Drug Evaluation again

Apply for testing.

32. What is the format of the XML format file submitted through the applicant window?

Path generated?

Answer: Extensible Markup Language (XML) is a markup language that defines

A set of rules for encoding documents in a human-readable and machine-readable format.

XML format files that comply with E2B (R3) requirements must pass through a professional electronic system

generate.

6. Questions and answers related to other issues

33. How can I purchase the MedDRA dictionary? How to pay

cost?

Answer: The MedDRA dictionary needs to be ordered through the MedDRA official website

For detailed information on subscription methods, charging methods and other information, please log in to MedDRA official website

website to find out.

34. Is the MedDRA dictionary used for rapid reporting required?

When to update? Will only the latest version be supported?

Answer: The Center for Drug Evaluation will conduct twice a year in accordance with the time specified by MedDRA.

Updated to support the latest and previous versions. Applicants are advised to always use the latest version

row encoding.

35. Daily encounters with questions related to rapid reporting during drug clinical trials

Question, what are the consultation channels and methods?

Answer: The following ways and methods can be used:

ÿEmail: ywjjxtwt@cde.org.cn

ÿCenter for Drug Evaluation website (www.cde.org.cn) ÿ Applicant Window ÿ Communication with feedback

7. References:

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