# Standards and procedures for rapid reporting of safety data during drug clinical trials

To implement the former State Food and Drug Administration's "Regulations on the Application of International Human Rights".
Announcement on the Level II Guidance Principles of the Drug Registration Technical Coordination Committee (Announcement No. 10 of 2018)
In accordance with the requirements of (No.), our center follows the ICH guidelines on pharmacovigilance [E2A, ...].
E2B (R3) and M1 drafted the "Safety Data During Drug Clinical Trials".
Rapid Reporting Standards and Procedures (hereinafter referred to as "these Standards and Procedures"), specifically as follows:
Down:

I. The applicant is granted permission to conduct drug (including chemical drugs, traditional Chinese medicine, and biological products) production.
Following clinical trials of [product name], for any events occurring during the clinical trials (including those within China)
(and overseas) all unexpected and serious (and suspected) connections to the investigational drug.
Adverse reactions (hereinafter referred to as "unexpected serious adverse reactions"), and this standard
In other cases as specified in the procedures, the provisions of this standard and procedures shall apply within the prescribed time.
Report to the National Drug Evaluation Agency within the specified time limit.

II. Serious adverse reactions refer to one of the following situations: (1) leading to death; (2)
"Life-threatening" refers to a critically ill patient facing an immediate risk of death, not a hypothetical situation.
In the future, if the condition worsens, it may lead to death; (3) it may result in hospitalization or prolonged hospitalization.
(4) Permanent or significant loss of function; (5) Teratogenicity or birth defects;

(6) Other significant medical events: decisions must be made using medical and scientific judgment.
Should other situations be reported more quickly, such as important medical events that may not be reported immediately?
Life-threatening, death, or hospitalization, but if medical measures are required to prevent such events.
One such situation is often considered serious. For example, in the emergency room...

Allergic bronchospasm that occurs at home or requires important treatment, and cachexia that is not hospitalized.

It may cause seizures, drug dependence, or addiction.

III. Unexpected adverse reactions refer to the nature and severity of adverse reactions.

Consequences or frequencies that differ from current information on the investigational drug (such as investigator's manuals)

The expected risks described in documents such as the Investigator's Handbook are provided as the primary document.

Safety reference information used to determine whether an adverse reaction is expected or unexpected.

For example: (1) Acute renal failure is listed as an adverse reaction in the investigator's manual, but trials have shown that...

If interstitial nephritis occurs during the process, it should be judged as an unexpected adverse reaction. (2) Liver

Inflammation is listed as an adverse reaction in the investigator's manual, but an acute severe case occurred during the trial.

Type 2 hepatitis should be considered an unexpected adverse reaction.

IV. During the clinical trial of the drug, the applicant determined whether the drug was compatible with the investigational drug.

Any unforeseen and serious adverse reactions that are not definitively related or suspected must be handled in accordance with this standard.

The program reports quickly as individual security reports.

Applicants and researchers do not [particularly in determining the causal relationship between adverse events and drugs]

When an agreement can be reached, either party may determine that a link to the investigational drug cannot be ruled out.

Such incidents should also be reported quickly.

V. The following situations are generally not included in the content of the rapid report: (1) Non-serious

Adverse events; (2) serious adverse events unrelated to the investigational drug; (3) serious but...

(4) When serious adverse events are the primary efficacy endpoint, the adverse events are expected to occur.

In such cases, it is not recommended that applicants submit individual case safety reports (ICSRs) to the National Medical Products Administration.

Product review agency report.

VI. The applicant is responsible for resolving any serious adverse reactions related to the positive control drug.

Determine whether to supply other drug manufacturers and/or directly to the National Medical Products Administration.

Departmental report. Applicants must report to the drug manufacturer or directly to the National Medical Products Administration.

Management reports such events. Adverse events related to placebos are generally not consistent with this.

Report adverse reactions quickly in accordance with the criteria.

VII. The content of safety reports for unintended serious adverse reactions should be in accordance with...

ICH E2B(R3): Management of clinical safety data: Case safety reporting

Report on requirements related to "Transmitted Data Elements". Relevant terminology should conform to ICH M1:

The code is coded according to the Medical Dictionary of Regulatory Activities (MedDRA).

8. The applicant is a drug clinical trial safety information monitoring and unexpected event monitoring agency.

The responsible party for reporting serious adverse reactions. The applicant should designate a specific person to be responsible.

Clinical trial safety information monitoring and serious adverse event reporting management should be developed;

Standard Operating Procedures for Clinical Trial Safety Information Monitoring and Serious Adverse Event Reporting

The process should be streamlined, and all relevant personnel should be trained; the most important aspects of the clinical trial process should be mastered.

New safety information should be promptly assessed for safety risks and communicated to relevant parties involved in the trial.

They are responsible for providing relevant information and for rapidly reporting any unexpected serious adverse reactions.

9. Upon becoming aware of a serious adverse event, the applicant should immediately take action against it.

The event undergoes a comprehensive analysis, assessment, and judgment. This is based on the nature of the serious adverse event.

(Category) Report to the National Drug Evaluation Agency expeditedly within the following timeframes:

(a) For unexpected serious adverse reactions that may result in death or endanger life, please apply.

The person seeking assistance should report the incident as soon as possible after first becoming aware of it, but no later than 7 days later, and subsequently...

Report and complete follow-up information within 8 days.

Note: The day the applicant first learns of the information is day 0.

(ii) For unexpected serious adverse reactions that are not fatal or life-threatening,

The applicant should report as soon as possible after first learning of the information, but no later than 15 days.

10. The start date for expedited reporting is the clinical trial approval date/National Drug Administration date.

The review agency implicitly approved the start date of the trial and the end date of the last domestic trial.

End date of follow-up. From the end of the clinical trial or the end of the follow-up period until obtaining review approval.

Serious adverse events occurring before the approval of the conclusion should be reported by the researcher to the applicant.

Any unexpected serious adverse reactions should also be reported promptly.

XI. After the initial report, the applicant should continue to monitor serious adverse reactions.

Relevant new information or updates to previous reports should be submitted promptly in the form of follow-up reports.

For changes to information, the reporting deadline is 15 days from the date the new information is obtained.

12. The National Drug Evaluation Agency shall use electronic standards that comply with ICH E2B(R3)

Sub-transmission method for receiving individual case safety data submitted by the applicant during drug clinical trials

After the sex report is submitted, an analysis and evaluation will be conducted, and modifications to the test will be proposed if necessary in accordance with relevant standards.

Opinions on plans, suspension or termination of drug clinical trials, etc.

Thirteen, apart from individual safety reports of unexpected serious adverse reactions.

In addition, applicants should also promptly report any other potentially serious security risks.

Report to the national drug review agency, and provide medical and scientific assessments for each situation.

Academic judgment. Generally speaking, for information that significantly affects the assessment of drug risk-benefit...

Information that may involve changes to drug usage or affect the overall drug development process.

All such information falls into this category, for example: (1) for known, serious adverse reactions

(2) The incidence rate increases, indicating clinical importance;

Obvious harm, such as ineffectiveness of the drug in treating life-threatening diseases; (3) in recent

Significant safety findings (such as carcinogenicity) in completed animal studies.

XIV. Non-relevant information related to the investigational drug obtained by the applicant from other sources

Information on anticipated serious adverse reactions and other potential serious safety risks should also be provided.

A rapid report should be submitted to the national drug review agency.

15. Regardless of whether it is a domestic or overseas case safety report or other potential [issues].

All reports of serious security risks should be submitted in Chinese.

XVI. Individual security reports and other reports of potentially serious security risks

The application for clinical trial of the drug should be clearly indicated in the report.

In individual safety reports, the clinical trial application acceptance number is entered in the data.

Element Gk3.1 Approval Number/License Number (Gk3.1 Authorisation /

Under the "Application Number" field.

17. Electronic transmission method for individual adverse reactions:

1. Submit via GATEWAY

The applicant applies for a GATEWAY account and conducts an electronic transmission test.

Once successful, proceed with the formal submission.

2. Submission via XML file

Applicants should log in to the official website of the National Center for Drug Evaluation.

(www.cde.org.cn), register an account in the "Applicant's Window" section, on the left side.

Submit an XML file using the "Pharmacovigilance Submission" option under the menu bar.

You may choose either of the two methods above. See the attachment for detailed instructions.

18. Rapid reporting of other potentially serious security risks can be done through [method/mechanism].

Please send it via email to: lcqjywjj@cde.org.cn.

Attachment: Electronic case safety report conforming to ICH E2B(R3) requirements

Transmission technology documents

Center for Drug Evaluation

April 27, 2018

appendix:

# Electronic transmission technical documentation for individual case safety reports conforming to ICH E2B(R3) requirements

## I. Preparation of Individual Case Safety Reports (ICSRs) by the Sender

1. Users first need to log in to the National Center for Drug Evaluation (hereinafter referred to as the Center for Drug Evaluation).

Register an account on the official website of the Center for Evaluation and Review (www.cde.org.cn).

2. After registering an account, users can submit their applications using one of the following two methods.

ICSR Report: Gateway to Gateway; Applicant

Upload XML files to the window.

3. Both methods require users to perform corresponding testing steps to ensure correctness.

The ICSR submitted in this manner complies with ICH E2B(R3) and the relevant requirements of the Center for Drug Evaluation.

specification.

## II. Submission of Individual Case Safety Reports (ICSR)

In accordance with E2B(R3) guidelines, the electronic transmission and submission of ICSRs should

Provides the specified data elements. Electronic transmission and delivery rely on XML schemas.

Information standards to achieve [something] throughout the entire lifecycle of a drug, including clinical trials and research.

Safety monitoring during the research period and ongoing.

Note: If the initial ICSR was submitted in paper form, but subsequent ICSRs were submitted electronically...

If the submission is in subform, its ICSR statement should be declared in the subsequent electronic submission's ICSR narrative section.

The initial report was submitted in paper form.

**Method 1: Submit steps via Gateway to Gateway**

1. Submit a test report:

(1) Fill out the "ICSR Electronic Transmission Account Application Form" and send it to [email address].

Register at E2Btest@cde.org.cn for electronic reporting of individual security cases.

Enter your test account. See attached table for details.

(2) After receiving the email application, the staff of the Center for Drug Evaluation will reply as follows:

The following information is provided for companies and the Center for Drug Evaluation to establish electronic transmission links:

ÿ Contact information for the Center for Drug Evaluation (related to ICSR electronic transmission)

For inquiries, please contact us via email at E2Btest@cde.org.cn.

ÿ The URL for the Center for Drug Evaluation to receive test reports; companies need to configure the URL.

Electronic data exchange in the sender's drug safety database

In the interchange, EDI) module;

ÿ The digital certificate from the Center for Drug Evaluation needs to be configured by the company on the sending side.

The server where the EDI module is located;

ÿ The identification ID used by the Center for Drug Evaluation during electronic transmission.

This corresponds to element N.2.r.3, the information receiver identifier, in the E2B(R3) specification.

For identification purposes, enterprises need to configure this ID in the sender's EDI module for use.

The recipient of the transmitted file is identified as the Center for Drug Evaluation.

(3) The user sends a test ICSR report to verify the interoperability between modules.

It is valid and capable of transmitting electronic documents that comply with E2B (R3) requirements, upon receipt.

Once the Center for Drug Evaluation confirms the validity of the test report with an electronic receipt, the system is successfully established.

Formal transmission of ICSR data connection.

2. Submit a formal report:

(1) Fill out the "ICSR Electronic Transmission Account Application Form" and send it to [email address].

Register at E2Btest@cde.org.cn for electronic transmission of individual security reports.

Official account. See attached table for details.

(2) After receiving the email application, the staff of the Center for Drug Evaluation will reply as follows:

The following information is provided for companies and the Center for Drug Evaluation to establish electronic transmission links:

ÿ Contact information for the Center for Drug Evaluation (related to ICSR electronic transmission)

For inquiries, please contact us via email at E2Btest@cde.org.cn.

ÿ The URL for the Center for Drug Evaluation to receive formal reports; companies need to configure the URL.

Electronic data exchange in the sender's drug safety database

In the interchange, EDI) module;

ÿ The digital certificate from the Center for Drug Evaluation needs to be configured by the company on the sending side.

The server where the EDI module is located;

ÿ The identification ID used by the Center for Drug Evaluation during electronic transmission.

This corresponds to element N.2.r.3, the information receiver identifier, in the E2B(R3) specification.

For identification purposes, enterprises need to configure this ID in the sender's EDI module for use.

The recipient of the transmitted file is identified as the Center for Drug Evaluation.

(3) After receiving the email, the user sends a formal ICSR report to verify the model.

Inter-block communication is effective and can transmit electronic documents that comply with E2B (R3) requirements.

Once the electronic receipt confirming the validity of the official report is received from the Center for Drug Evaluation, the file will be ready.

This means that a data connection for formal transmission of ICSR has been successfully established.

**Method 2: Submitting an XML file via the applicant's portal**

1. Submit a test report

(1) The user generates an XML-formatted test result in their drug safety database.

Try ICSR.

(2) Register the applicant's window account with the Center for Drug Evaluation.

(3) Send the above ICSR as an email attachment to

Emails should be sent to E2Btest@cde.org.cn with the subject line "E2B (R3) Test Report".

The email body states that the report is for testing purposes and provides:

ÿ A unique identifier for the enterprise in the XML file (this ID corresponds to...)

Element N.2.r.2 (message sender identifier) in the E2B(R3) specification (drug review)

The evaluation center will configure this ID in the system's receiving module as part of the formal submission.

A unique identifier for a company;

ÿ Company name, applicant's account on the online application platform, and company type (whether it is a legitimate business).

(Same as research organizations or drug safety database providers).

ÿICSR Electronic Transmission Account Application Form.

2. Submit a formal report

(1) The user generates a positive XML format file in their drug safety database.

Formula ICSR.

(2) Send the following information as an email attachment to [email address].

Emails should be sent to E2Btest@cde.org.cn with the subject line "E2B (R3) Official Report".

The email body stated that it was a formal report and provided the following:

ÿ A unique identifier for the enterprise in the XML file (this ID corresponds to...)

Element N.2.r.2 (message sender identifier) in the E2B(R3) specification (drug review)

The evaluation center will configure this ID in the system's receiving module as part of the formal submission.

A unique identifier for a company;

ÿ Company name, applicant's account on the online application platform, and company type (whether it is a legitimate business).

(Same as research organizations or drug safety database providers).

ÿICSR Electronic Transmission Account Application Form.

(3) Log in to the applicant's window and submit the formal ICSR in the corresponding section.

III. The Center for Drug Evaluation receives and verifies ICSRs.

After receiving the ICSR from the company, the Center for Drug Evaluation will send the first...

A receipt indicates that the user successfully transmitted the data and that the Center for Drug Evaluation has received the report.

Next, the system will perform a secondary verification of the ICSR to determine whether it meets the E2B requirement.

(R3), and the Center for Drug Evaluation will return a second result based on the second verification result.

A response regarding ICSR compliance; some requirements for E2B (R3) in the document.

Any omissions or errors in the compliance information will also be listed in the Center for Drug Evaluation's response.

The system will reject reports that do not meet the most basic requirements of E2B (R3).

Receive and send a rejection receipt to the sender.

IV. The Center for Drug Evaluation sends a receipt to the ICSR tester.

1. If the user does not receive any notification from the Center for Drug Evaluation within 24 hours of submission,

If no receipt is received, it indicates that the network connection has failed and requires testing and communication with the Center for Drug Evaluation.

Is the network connection broken?

2. If a user receives a rejection receipt after submitting their application, they should refer to the information in the receipt.

The pointed-out cases of correcting E2B (R3) transmission errors are in accordance with relevant regulations.

The case must be submitted again within the submission deadline; and the resubmission must use a [specific format].

Resubmit the ICSR with a new, unique file identifier (instead of a case identifier).

V. Precautions

1. The ICSR transmissions received by the Center for Drug Evaluation are based on AS2.

(HTTPS) transport protocol.

2. ICSR document attachments: Multiple documents can be provided in an ICSR.

Title (C.1.6.1.r) and document title (C.4.r.1), along with related materials. ICSR

The attachment can be viewed as an embedded file encoded in base64, used in drug review.

The center allows PDF as the file attachment format.

3. If the information filled in by the user in the ICSR electronic transmission account application form is consistent with...

If the information provided by the applicant on the Center for Drug Evaluation (CDE) website is inconsistent, the CDE will reject the application.

Collect their ICSR electronic transmission account application form.

Appendix

ICSR Electronic Transmission Account Application Form

| | |
|---|---|
| User authentication information | |
| Company Name \| | |
| Unified Social Credit Code \| Applicant's Window | |
| Account \| Applicant's Window | |
| Contact Person Name \| Applicant's Window Contact | |
| Person Telephone \| Applicant's Window Email | |
| | |
| ICSR Electronic Transmission Contact Information | |
| Main contact person's name (for contacting ICSR regarding electronic transmissions) | |
| Main contact person's phone number (must be reachable) | |
| Primary contact's email address (must be accessible) | |
| Backup contact person's name, | |
| backup contact person's phone | |
| number, backup email address. | |
| Electronic transport parameters | |
| The URL for sending the test report, and the URL for receiving the electronic receipt from the National Center for Drug Evaluation (usually obtainable from the company's drug safety database). (Found in the EDI module) | |
| In electronically transmitted information, the enterprise's identification ID (this ID corresponds to element N.2.r.2, the information sender identifier, in the E2B R3 specification). | |
| Digital certificate information and enterprise firewall information for digitally signing and encrypting transmitted reports: 1) If | (Please submit your digital certificate as an attachment in the email, such as a certificate with the .cer extension.) |
| SSL certificate is used, please provide the username and password. 2) If a proxy server is used, please provide the proxy server information. | |

Note: When uploading ICSR through the Applicant's Window, it is not necessary to fill in the "Required Electronic Transmission Parameters". However, when submitting via Gateway to Gateway, it is mandatory to fill in the electronic transmission parameters.