Provisional Translation (as of June 2022) *

PMDA/CPE Notification No. 0401003
PMDA/CRS Notification No. 0401001
April 1, 2022

To: Prefectural Health Department (Bureau)

Director of Center for Product Evaluation,
Director of Center for Regulatory Science,
Pharmaceuticals and Medical Devices Agency

Technical Conformance Guide on Electronic Study Data Submissions

Handling of submission of electronic study data for new drug applications has been notified in the notifications 1. and 2. in the attachment (hereinafter referred to as "former director notifications"). More detailed matters and precautions regarding submission of electronic study data for new drug applications have been notified in the "Technical Conformance Guide on Electronic Study Data Submissions" (PMDA/OAE Notification No. 0427001, by the Director of the Advanced Review with Electronic Data Promotion Group, Pharmaceuticals and Medical Devices Agency, dated April 27, 2015; hereinafter referred to as "former notification").

Upon abolishment of the former director notifications and release of notifications 3. and 4. that notify on handling of submission of electronic study data for new drug applications, we have decided to compile more detailed matters and precautions regarding submission of electronic study data for new drug applications as shown in the appendix; therefore, we ask you to inform manufacturers and sellers placed under your administration.

In accordance with the release of this notification, the former notification is abolished.

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Attachment

1. Basic principles on submission of electronic study data

- Basic Principles on Electronic Submission of Study Data for New Drug Applications (PFSB/ELD Notification No. 0620-6, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated June 20, 2014) (abolition, dated April 1, 2022)
- Question and Answer Guide Regarding "Basic Principles on Electronic Submission of Study Data for New Drug Applications" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 18, 2020) (abolition, dated April 1, 2022)

2. Practical operations on submission of electronic study data

- Notification on Practical Operations of Electronic Study Data Submissions (PFSB/ELD Notification No. 0427-1, by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated April 27, 2015) (abolition, dated April 1, 2022)
- Question and Answer Guide Regarding "Notification on Practical Operations of Electronic Study Data Submissions" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated March 18, 2020) (abolition, dated April 1, 2022)

3. Handling of the submission of electronic study data

- Notification on Handling of Submission of Electronic Study Data for New Drug Applications (PSEHB/PED Notification No. 0401-10, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022; referred to as "notification on electronic study data" in the Appendix)
- Question and Answer Guide Regarding "Notification on Handling of Submission of Electronic Study Data for New Drug Applications" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022)

4. New drug applications using the gateway system

- New Drug Applications Using the Gateway System (PSEHB/PED Notification No. 0401-7, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated April 1, 2022; referred to as "notification on gateway application" in the Appendix)

Appendix

Technical Conformance Guide on Electronic Study Data Submissions

1. Introduction

1.1 Purpose

Handling of the submission of electronic study data for new drug applications has been described in the notification on gateway application, notification on electronic study data and its question and answer guide. More detailed matters and precautions regarding the submission of electronic study data are provided in this guide.

In addition, detailed matters and precautions concerning the submission of related electronic files, including the eCTD, shall be described together in this guide.

1.2 Scope

The scope of this guide will include detailed matters and precautions on the submission of electronic study data for applications, and detailed matters and precautions regarding the submission of electronic files related to the subject product, including the eCTD. Various lists, tools, and links for the necessary files related to the content of this guide will be posted separately on the PMDA's website (https://www.pmda.go.jp/), which should also be referred to.

1.3 Definitions of terms

The system of terms used in this guide is shown in Attachment 1.

The terminology used in this guide, in principle, is the same as that used in the notification on gateway application and the notification on electronic study data.

2. Method of using the system for electronic study data submission

2.1 Method of using the gateway system

An application/review system and its related system that are used for electronic study data submission (hereinafter referred to as "gateway system") are available from the URL below. Please refer to the "Information on the Gateway System" and the operation manual for the gateway system on the PMDA's website for information on the electronic certificate and other technical information required for using the gateway system and details on the method of its use.

(Gateway system: https://esg.pmda.go.jp/Ssk/comn001p01.init).

3. Submission of electronic study data

3.1 Basic flow of the submission of electronic study data

The applicant must confirm with the PMDA on the scope of the submission of electronic study data and the planned date of a new drug application by utilizing clinical trial consultations, a consultation on preparation of submission of electronic study data, and a pre-NDA consultation, etc., if necessary. Applicants must outline the contents of electronic study data that will be submitted to the NDA using the "Explanation of Electronic Study Data (Form A)" on the PMDA's website. This document should preferably be submitted at the time of the pre-NDA consultation that will be conducted before the submission of electronic study data.

In accordance with the notification on gateway application, the applicant shall make an advance notice of the application from the gateway system and obtain the information (e.g., in the case of the eCTD, the eCTD receipt number) required to manage the electronic files to be submitted. The applicant shall then enter and register the information related to the application and send the electronic files necessary for

the application [such as application form data (hereinafter referred to as "FD application data"), eCTD, and electronic study data] using the gateway system.

3.2 Method of the submission of electronic study data

When submitting electronic study data, the applicant must use the gateway system in accordance with the notification on gateway application. For the method of submission when referencing electronic study data from the XML message of the eCTD, also please refer to the "Approval Application with Electronic Common Technical Document (eCTD)" (PSEHB/PED Notification No. 0705-1, by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated July 5, 2017; hereinafter referred to as "eCTD v4 notification").

3.3 Submission of electronic study data via the gateway system

When submitting electronic study data, the applicant must register, select, or enter the following additional information using the gateway system or XML message of the eCTD. Examples of such additional information are as follows. Not all items need to be registered, selected, or entered at each submission.

- Gateway receipt number
- Version of the validation rule
- Information for identifying to which file the data is appended [such as eCTD receipt number, submission serial number, CTD section number (up to here, only applicable to applications with eCTD), study number, study title]
- Identifier of each file (UUID defined by ISO/IEC 11578:1996 and ITU-T RecX.667 | ISO/IEC 9834-8:2005)
- Position of electronic study data (such as addition, replacement, deletion)
- Identifiers of data subject to replacement or deletion
- File path
- Data analysis type
- Explanation of the file content

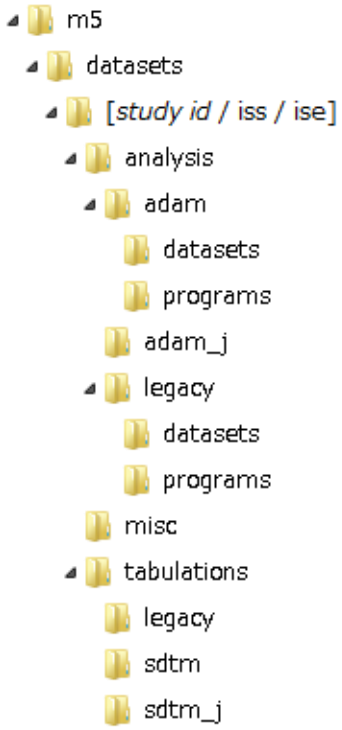
After registering, selecting, or entering the above details, except for when referencing electronic study data from the XML message of the eCTD, register the "m5" folder containing electronic study data to be submitted using the gateway system and send it. When referencing electronic study data from the XML message of the eCTD, register the eCTD receipt number folder and send it as eCTD. For the details on operating the gateway system, please refer to the operation manual for the gateway system.

3.4 File size of electronic study data

Of electronic study data to be submitted, PDF files must not exceed the maximum file size of PDF specified in the eCTD v4 notification. An applicant should consult the PMDA beforehand if the total file size in a single operation and/or the size of each file of electronic study data other than PDF files exceed the upper limit. For the upper limit for the file size, please refer to the operation manual for the gateway system.

3.5 Folder structure

In principle, electronic study data should be submitted after storing it in the following folder structure, and no additional subfolders should be created. If storing the data in the following folder structure is difficult, the applicant must consult the PMDA beforehand and make a submission after agreeing on the folder structure and the storage of files. Hierarchies down to "m5¥datasets¥[*study id* / iss / ise]"cannot be changed.



Note the following points when storing electronic study data into the abovementioned folder structure.

- The path length counting from the “m5” folder, including the file name, must be 160 characters or shorter.
- Folder names should be 32 characters or fewer, and must be comprised of the following characters.
  - Alphabetic characters from “a” to “z” [U+0061 to U+007A]
  - Numbers from “0” to “9” [U+0030 to U+0039]
  - Low line “_” [U+005F]
  - Hyphen-minus “-” [U+002D]
- File names should be 32 characters or fewer for datasets and 64 characters or fewer for files other than datasets (including the extension), and the name excluding the dot and the extension must be comprised of the following characters. For characters to be used for file names, please refer to the operation manual for the gateway system.
  - Alphabetic characters from “a” to “z” [U+0061 to U+007A]
  - Numbers from “0” to “9” [U+0030 to U+0039]
  - Low line “_” [U+005F]
  - Hyphen-minus “-” [U+002D]
- The reviewer’s guide, define.xml, and style sheet must be stored in the same folder as their corresponding datasets. The style sheet should display the information in the define.xml, which is to be submitted to the PMDA.
- If there is no file to store the data, this folder should not be created.
- When storing electronic study data in the field of clinical pharmacology in a format other than the CDISC standard, one example is to create and store it in a “cp” folder under the “analysis” folder as mentioned in the table below. In such a case, there will be no special restriction on the folder structure within the “cp” folder. The method of storing the data is not limited to that mentioned above. However, regardless of the method of storage, the above considerations on path

length, folder name, and file name must be followed. It is preferable to consult the PMDA beforehand on the method of storing the data.

The usage method of each folder is as follows.

Folder name	Hierarchy	Description
m5	1	Top-level folder of electronic study data. This folder should not contain any files other than subfolders.
datasets	2	Folder for storing electronic study data. This folder should not contain any files other than subfolders.
[*study id* / iss / ise]	3	Folder created for each study or for each integrated analysis results. Folder name should be the study number (such as study123) or the type of analysis (such as iss, ise) that allows the unique identification of each study. This folder should not contain any files other than subfolders
analysis	4	Folder for storing analysis datasets and programs. This folder should not contain any files other than lower folders
adam	5	Folder for storing ADaM datasets and programs. This folder should not contain any files other than lower folders
datasets	6	Folder for storing ADaM datasets.
programs	6	Folder for storing programs related to the creation of ADaM datasets, tables, or figures.
adam_j	5	Folder for storing the Japanese dataset that corresponds to the alphanumeric ADaM dataset. This folder should not contain any files other than the Japanese ADaM dataset.
cp	5	Folder for storing electronic study data on clinical pharmacology in formats other than the CDISC standard.
legacy	5	Folder for storing analysis datasets and programs in formats other than ADaM. This folder should not contain any files other than lower folders.
datasets	6	Folder for storing analysis datasets in formats other than ADaM.
programs	6	Folder for storing programs related to the creation of analysis datasets in formats other than ADaM, tables, or figures.
misc	4	Folder for storing data which is not appropriate for storage in the analysis or tabulations folder.
tabulations	4	Folder for storing datasets in which subject data and study-related information are displayed in a tabulation format. This folder should not contain any files other than lower folders.
legacy	5	Folder for storing non-SDTM datasets which are in a list format.
sdtm	5	Folder for storing SDTM datasets.

Folder name	Hierarchy	Description
sdtm_j	5	Folder for storing the Japanese dataset that corresponds to the alphanumeric SDTM dataset. This folder should not contain any files other than the Japanese SDTM dataset.

3.6 Validation of electronic study data

Electronic study data, which are submitted via the gateway system, will be validated according to the type of data. The results of the validation will be notified to the applicant via the gateway system. Electronic study data, which violate the rules shown in 3.6.1 (a), should be corrected prior to the submission of a new drug application and, preferably, all data should be resubmitted.

If an error occurs during data transmission or while operating the gateway system, please contact the gateway system help desk for directions.

3.6.1 Validation of data conforming to the CDISC standards

The PMDA will perform validation of data that conform to the CDISC standards using Pinnacle 21 Enterprise.

The rules used for validation have been classified by the level of importance taking into consideration the characteristics of each rule and based on conformity to the standards, ease of use of the data in review, quality of the clinical study data which the PMDA should know beforehand, and future uses of the clinical study data by the PMDA. The levels of importance are shown below.

(a) Rules which, if violated, will cause the review to be suspended until corrections have been made

Very basic rules such as the presence/absence of necessary datasets for each clinical study

(b) Rules which, if violated, will require an explanation

In many cases, these rules are clearly stated in each standard and implementation guide, and if violated, the applicant should explain in the reviewer's guide about the reason for the violation and the reason why it is not possible to correct it.

(c) Rules which, even when violated, will not necessarily require any explanation

The reason for the violation possibly is requested separately for the above (c) from the perspective of the quality of the clinical study data.

Details of the environment in which the PMDA performs validations, individual rules and their importance are published on the PMDA's website. Before submitting electronic study data, the applicant should perform a validation, and should take the necessary action for any violations that are identified. Please keep in mind that these rules may be revised and that validation should always be performed after confirming the latest information. If any rules are revised, the content of the revision will be available for a certain period before the revised rules are applied.

4. Electronic study data to be submitted

4.1 CDISC-conformant electronic study data and relevant documents

4.1.1 Datasets to be submitted

4.1.1.1 Overview

CDISC standards should be used for the submission of clinical study data. For the latest standards and implementation guide (IG) of CDISC and the

development status, please refer to the CDISC's website (https://www.cdisc.org/).

The CDISC provides SDTM as the standard for datasets comprising clinical study data collected from the CRF and other records in a tabulation format and ADaM as the standard for analysis datasets. Data should be summarized using the designated variables and submitted in accordance with the versions of SDTM and ADaM standards and IG that are accepted by the PMDA.

To avoid the complication of having to convert the collected data into a CDISC-conformant format upon application, it is preferable to decide on the method of data collection and analysis procedures that will conform to these standards from the planning stage of the clinical study. However, these standards do not indicate the items of the clinical study data required for the review. Therefore, the items of data to be collected from each clinical study must be established, which enables efficacy and safety evaluations of the drug and ensures the subjects' safety, by taking into consideration the characteristics of the target disease and the drug. If there are multiple methods of implementation based on the clinical study design or characteristics of the data to be collected or if some aspects of the dataset cannot or may not conform to the standards or IG upon creating a dataset conforming to these standards, the applicant should consult the PMDA beforehand.

CDISC standards, controlled terminologies to be used, and terms defined in dictionaries should be used without modifying spelling or notation, such as capital and small letters, when creating datasets.

4.1.1.2 SDTM datasets

The SDTM dataset is to be submitted, after the data collected from the CRF and other records are stored into the domain using variables designated by the version of SDTM and SDTM IG. The applicant may manage the clinical study data using their own unique format that includes SDTM, but even in such cases, the dataset to be submitted must be converted into formats that are in accordance with SDTM and SDTM IG.

In SDTM, the variables are classified into Required, Expected, and Permissible. If the variables contain collected data, the data for all variables must be submitted to the extent possible, regardless of the classification. Of the Permissible and Expected variables, the following must be submitted to the extent possible.

- Baseline flags (such as laboratory results, vital signs, ECG, pharmacokinetic concentration, and microbiology results)
- EPOCH designator (variables that designate the period)
- If the dataset contains --DTC, --STDTC, and --ENDTC variables, the corresponding Study Day variables (--DY, --STDY, and --ENDY)

SDTM dataset stores the data obtained in the study and does not include values used to impute missing data. Imputed data should be included in the ADaM dataset.

Basic rules of SDTM should be followed, for example, dates must be in accordance with ISO 8601 format, --DY must not contain 0, and even when the data was collected as Yes/No in the CRF, it must be stored as Y/N in SDTM dataset.

USUBJID has been prepared as a variable for storing the unique ID assigned to each individual subject across the entire application. It enables the data of one subject in multiple studies, for example, in a phase III study and the subsequent

long-term study, to be summarized. Therefore, consideration should be given to ensure that each subject has the same USUBJID across all the studies in the application to the extent possible.

In SDTM, the domains of the Trial Design Model, such as TS domain, store information on the designs of clinical studies and thus contain useful information on the characteristics of the clinical studies. Its data should, therefore, be stored in accordance with the IG to the extent possible and be submitted.

In SDTM, it is possible to set a series of datasets called SUPPQUAL to include variables that are not specified in SDTM. These datasets may be used for data that cannot be allocated to each of the domains of SDTM. However, basically, variables related to main analyses should not be included in such datasets. If an applicant is considering to include a variable which is not mentioned specifically in the IG but may be important for the review in the SUPPQUAL, the applicant should consult the PMDA beforehand, and if the variable has been included in the SUPPQUAL, this should preferably be explained in the reviewer's guide.

Depending on the characteristics of the collected data, it may not fit into an existing domain of SDTM. In such a case, it is acceptable for the applicant to create a custom domain. To perform this, the applicant must confirm that the data does not fit into existing domains, then create a custom domain according to the SDTM IG, and store the data under this domain. Explanation of the custom domain, together with the reason why it was necessary, should be described in the reviewer's guide.

4.1.1.3 ADaM datasets

The analysis datasets should be submitted after they are constructed in accordance with ADaM. It is not necessary to submit ADaM datasets for all analyses described in the statistical analysis plan. However, ADaM datasets should be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, such as primary efficacy analysis and secondary efficacy analyses (secondary analyses of primary variable and analyses of key secondary variables), primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety. The applicant should preferably consult the PMDA beforehand on the sufficiency of the datasets to be submitted. Even when the analysis results in the clinical study report had been created using datasets other than ADaM datasets, for analyses related to important results on efficacy and safety and the rationales for setting of the dosage and administration mentioned above, the analysis datasets based on ADaM that can reproduce these results should be submitted. It is not necessary to submit additional analysis datasets for analyses that the applicant performed after the application in response to inquiries.

In ADaM, there is a dataset called Analysis Data Subject Level (ADSL), which contains subject level information, and this must be submitted for each study for which the ADaM datasets have been submitted. To make each analysis using the ADaM dataset easier, the core variables, including all covariates described in the protocol that are generally included in the ADSL dataset, in principle, should be included in each ADaM dataset. Examples of such variables include covariates, study (protocol number), study site (site number), region, country, assigned treatment, sex, age, race, analysis population flags, and other important baseline demographic variables.

Please keep in mind that ADaM datasets other than ADSL can consist of various variables depending on the nature of the individual target analysis, and it is, therefore, important to explain the content of these datasets in the definition document and the reviewer's guide.

If the variables used in the SDTM dataset are also used in the ADaM dataset, these variables must have the same attributes and content.

4.1.1.4 File formats of datasets

The SDTM and ADaM datasets that conform to the CDISC standards should be submitted in the SAS XPORT file transport format Version 5 (hereinafter referred to as SAS XPORT format), which is the data transport format released by the SAS Institute, and as one file per dataset. The SAS CPORT Procedure must not be used when creating XPORT transport files by the SAS system. Similarly, for datasets that contain variables written in Japanese because it was considered necessary and appropriate (hereinafter referred to as Japanese items), the files should be in the SAS XPORT format, and the character sets or the encoding scheme used to create the dataset should be described in the reviewer's guide.

The file name and the dataset name must be the same for the SDTM and ADaM datasets.

4.1.2 Definition documents and other appended documents of datasets

4.1.2.1 Definition documents of datasets

The definition documents of the SDTM and ADaM datasets in the Define-XML format by the CDISC should respectively be created into the XML format files containing references to the style sheets that enable their contents to be displayed and stored in the same folder as their corresponding datasets, together with these style sheets. The file name of the definition document should be "define.xml". The definition document should include the definitions of datasets, variables, possible values of variables, and controlled terminologies and codes. The information on controlled terminologies and dictionaries should include their versions.

In order for the review of clinical study data to progress smoothly, it is important that the relationship between the analysis results shown in the application documents and the analysis datasets is easily understandable. Therefore, the definition documents of the ADaM datasets should preferably include Analysis Results Metadata, which shows the relationship between the analysis results and the corresponding analysis dataset and the variables used, for the analyses performed to obtain the main results of efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, shown in 4.1.1.3. The Analysis Results Metadata of each analysis should preferably include the following items.

- Figure or table numbers and titles showing the analysis results displayed in the clinical study report
- Purpose and reasons for performing the analysis
- Parameter name and code to be used
- Variables subject to analysis
- Dataset to be used
- Selection criteria for the records subject to analysis
- Corresponding description in the statistical analysis plan, analysis program name, and summary of the analytical methods
- Extract of the analysis program corresponding to the analysis method

For the format of the Analysis Results Metadata, the applicant should refer to the Analysis Results Metadata Specification for Define-XML by the CDISC to the extent possible, but if it is difficult to include it into the definition document, it is possible to submit it as a separated file in PDF format, as specified in the eCTD v4 notification. The explanations in the definition document may be written in Japanese.

4.1.2.2 Annotated CRF

The Annotated CRF shows the relationship between each item of data collected from the CRF and the variables included in the dataset. For datasets that conform to the CDISC standards, SDTM variables will be used as variables that correspond to the items in the CRF. For the method of annotating, please refer to the SDTM Metadata Submission Guidelines (SDTM-MSG) by the CDISC.

Data collected from the CRF should preferably be stored in the SDTM dataset whenever possible, prior to submission. However, if there are items of data that are not going to be submitted, it should be made clear in the Annotated CRF that the data is not included in the submitted dataset, and the reason why this data was not included should be provided in the reviewer's guide. However, it is not necessary to perform this if the reasons are obvious.

The file format of the Annotated CRF, in principle, should be a PDF, as specified in the eCTD v4 notification, and the file name should be "acrf.pdf". In principle, it should be stored in the same folder as SDTM datasets.

4.1.2.3 Reviewer's guide

To promote the understanding of the content and characteristics of the datasets by reviewers during the review and enable the applicant to explain about the utilization status of and conformance to the data standards when creating the datasets, a dataset definition document as well as a reviewer's guide must be created for each of the SDTM and ADaM datasets, which, in principle, should be stored in the same folder as their corresponding datasets prior to submission.

In principle, the following items should be included in the reviewer's guide for the SDTM dataset.

- Clinical study name, protocol number
- Explanation of the clinical study design
- Standards, controlled terminologies, and dictionaries used when creating datasets and their versions (SDTM, SDTM IG, SDTM Controlled Terminology, Define-XML, MedDRA, and WHODrug Global)[1]
- Explanation of the annotated CRF
- List of datasets to be submitted
  - SDTM datasets of the trial design
  - SDTM datasets of the subject data (including information about custom domains, SUPP, and use of Japanese in the datasets and SUPP)
  - Other datasets to be submitted
- Explanation of the subject data (including explanation of custom domains)
- Information on conformance to the data standards
  - Validation tool used for the validation and its version
  - Version of the validation rules used for the validation
  - Explanation on conformance to the data standards (explanation of the

[1] If the version used for the validation differs from that used for the dataset creation, the version used for validation should be described as "Information of conformance to the data standards".

validation results including the identification number and importance of a rule with a detected violation)

In principle, the following items should be included in the reviewer's guide for the ADaM dataset.

- Clinical study name, protocol number
- Explanation of the clinical study design related to the analysis datasets
- Standards, controlled terminologies, and dictionaries used when creating datasets and their versions (ADaM, ADaM IG, ADaM Controlled Terminology, Define-XML, MedDRA, and WHODrug Global)[2]
- Considerations related to multiple analysis datasets
- Considerations on creating the analysis datasets
- List of datasets to be submitted
  - ADaM datasets (including information that uses Japanese)
  - Other datasets to be submitted
- Explanation of the datasets
- Information on conformance to the data standards
  - Validation tool used for the validation and its version
  - Version of the validation rules used for the validation
  - Explanation on conformance to the data standards (explanation of the validation results including the identification number and importance of a rule with a detected violation)
- Information on the program
  - Analysis environment and software used
  - Explanation of programs that were used to create the ADaM datasets to be submitted and programs for analyses (if they cannot be submitted, specifications that show the analysis algorithm) to be submitted

When creating reviewer's guides for the SDTM and ADaM datasets, although no specific format for the reviewer's guide is provided as the CDISC standards, materials that the applicant may refer to are published.[3]

Each document should in principle be created as a PDF, as specified in the eCTD v4 notification, and the files for SDTM and ADaM should preferably be named "study-data-reviewers-guide.pdf" or "csdrg.pdf", "analysis-data-reviewers-guide.pdf" or "adrg.pdf", or the like, so that their contents are identifiable. The reviewer's guide may be written in Japanese.

4.1.3 Version of standards to be used

When creating the dataset and the definition document conforming to the CDISC standards, please refer to the PMDA's website for versions of the CDISC standards, controlled terminologies, and dictionaries that are accepted by the PMDA. Acceptance of versions is judged based on the date of submission described in the new drug application by the applicant.

It is sufficient to use different versions within the same application, but the same version must be used within the same clinical study. If the applicant had referred to other versions for certain domains within the same clinical study, the version used and the reason for using that version must be explained in the reviewer's guide.

[2] If the version used for the validation differs from that used for the dataset creation, the version used for validation should be described as "Information of conformance to the data standards".

[3] Regarding the reviewer's duide for SDTM datasets and ADaM datasets, the latest templates provided below can be used. https://advance.phuse.global/display/WEL/Deliverables

Datasets of integrated analyses of multiple clinical studies should be created using the same version, even if the version used to create the dataset of each clinical study was different. When standardizing the version, the reason that the specific version was chosen and considerations for converting to a different version should be described in the reviewer's guide. In cases where the version standardization is difficult and different versions are unavoidably referred to in the same analysis, describe in the reviewer's guide whether the difference between versions used affects the datasets to be submitted and, if it affects the datasets, detail the difference in the reviewer's guide.

4.1.4 Therapeutic area standards

To date, the Therapeutic Area Standards have been published for a number of diseases by the CDISC for storing data specific to each therapeutic area. These standards may be used for diseases for which standards have already been published. However, the standards used must be provided in the definition document of the datasets and the reviewer's guide.

4.1.5 Handling of data written in Japanese text

If variables had been collected in Japanese and there is a risk of losing certain information by translating it into English, the descriptions in Japanese are necessary and appropriate, and data written in Japanese (hereinafter referred to as Japanese data) may be submitted. Examples of variables that may contain Japanese texts are shown in Attachment 2 (but are not limited to these).

The method of storing Japanese data into datasets and the method of submission when a domain contains Japanese items, in principle, will be as follows. Examples are provided in Attachment 3.

- For the domain (dataset), two datasets: the Japanese dataset and a dataset comprising letter sets specified by ASCII such as alphanumeric characters (hereinafter referred to as alphanumeric dataset) should be created.
- In the Japanese dataset, only the Japanese items should be Japanese and the rest should be alphanumeric data, similar to that in the alphanumeric dataset.
- The Japanese dataset and alphanumeric dataset must be identical in structure, except for the data lengths of the Japanese items and the corresponding alphanumeric character sequence, and the two datasets must also have an identical record number and record order. The applicant only needs to submit the definition document for the alphanumeric dataset, and the definition document must be stored in the same folder as alphanumeric datasets.
- In the alphanumeric dataset, an English character sequence (such as "JAPANESE TEXT IN SOURCE DATA") which clearly states this is not the original data should be stored in the parts that correspond to the Japanese items. If the Japanese data must be stored by multiple variables or records due to restriction on the data length, this English character sequence must be stored in the corresponding records within the alphanumeric dataset.
- These English character sequences (such as "JAPANESE TEXT IN SOURCE DATABASE") must be consistent within the same study, and it must be stated clearly in the reviewer's guide or the definition document (define.xml) of the dataset.
- For parts that correspond to the questionnaires and code lists that contain Japanese text, an appropriate English translation or English character sequence must be stored. When storing English character sequences and distinguishing each of the character sequences, appropriate measures such as by attaching a number at the end of each sequence (example:

"JAPANESE TEXT IN SOURCE DATABASE 01" and "JAPANESE TEXT IN SOURCE DATABASE 02") should be taken, and the link with the original Japanese text should be shown in the reviewer's guide.

- Alphanumeric datasets must be included in the designated folder. The Japanese dataset corresponding to the SDTM dataset must be included in the "sdtm_j" folder, and the Japanese dataset corresponding to the ADaM dataset must be included in the "adam_j" folder. The same dataset name and label name must be used for the two datasets.
- For domains that do not contain Japanese items, only the alphanumeric dataset must be included in the designated folder, and the submitted data must not contain any duplicates.

In principle, for Japanese data, both SDTM and ADaM datasets should be stored by the above method before they are submitted, but if the applicant plans to submit data from clinical studies containing Japanese data, it is preferable to consult the PMDA beforehand on the scope of such data.

4.1.6 Submission of programs

4.1.6.1 Programs to be submitted

With respect to the programs related to electronic study data conforming to the CDISC standards, the programs used to create the ADaM datasets and programs used for analyses must be submitted for the analyses performed to obtain the important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration shown in 4.1.1.3. The main purposes of requesting the submission of these programs are to understand the process by which the variables for the analyses were created and to confirm the analysis algorithms. Therefore, it is not necessary to submit the programs in a format or content that allows the PMDA to directly run the program under its given environment. Also, although the programs to be submitted are not limited to specific software or versions, information on the environment in which the programs were created or run (operation system and software used and their versions) must be provided together in the reviewer's guide. If programs with macros had been used, the macro programs should preferably be submitted together. However, if submission of the macro program is difficult or submission of the program itself is difficult because the creation of the dataset or program was outsourced, the submission of specifications that show the analysis algorithm would be sufficient.

4.1.6.2 File format of the programs

As stated in 4.1.6.1, although the programs to be submitted are not limited to specific software or versions, the file name should include the extension attached by the analysis software. If the file name does not contain an extension, an explanation about the file format should be included in the reviewer's guide.

4.1.7 CDISC-conformant electronic study data on clinical pharmacology analyses

For the handling of CDISC-conformant electronic study data on clinical pharmacology analyses, please refer to 4.1.1 to 4.1.6. Points to be considered especially for those data are described in this section.

4.1.7.1 SDTM datasets

PP domain storing pharmacokinetic parameters should be submitted as well as PC domain storing drug concentration data, since the pharmacokinetic parameters themselves are considered as data to capture the characteristics of the drug. Creating RELREC dataset based on SDTM IG is preferable when

explaining the relationship of datasets between PC domain and PP domain. However, it would be also acceptable to explain those relationship in a document such as the reviewer's guide if it is difficult to create the RELREC dataset based on SDTM IG.

In the case where PC domain and PP domain are created by converting from datasets in a format other than CDISC standards, the traceability (the procedure of creating the PC domain and PP domain, the relationship between the information included in these domains, such as the relationship between the variables in PC domain and those in PP domain, etc.) should be explained in a document such as the reviewer's guide. In this case, PK parameters will not need to be recalculated from the PC domain for the purpose of the explanation of the traceability.

4.1.7.2 ADaM datasets

When ADaM datasets for PK or PK/PD analysis of blood and urine drug concentration are submitted, either a single dataset or multiple datasets would be acceptable as long as each analysis using the ADaM dataset can be performed easily without modification of the dataset.

When the datasets used for the analysis are in a format other than ADaM and are converted to ADaM datasets for the application, it is not necessary to submit the original datasets used for the analysis. However, if the original datasets are useful for explanation of traceability between datasets or contents of analysis, it may be submitted and used for the explanation.

4.2 Electronic study data on clinical pharmacology analyses

Matters that need to be followed with respect to the specific contents of the submission, including the "Explanation of electronic study data package on clinical pharmacology", as well as electronic study data on clinical pharmacology and programs are shown below.

4.2.1 "Explanation of electronic study data package on clinical pharmacology"

Since electronic study data on clinical pharmacology are stored in various folders and various file names, the PMDA will use the "Explanation of electronic study data package on clinical pharmacology" to review and use electronic study data submitted. "Explanation of electronic study data package on clinical pharmacology" is created by the PMDA based on the information about content of the clinical pharmacology study data provided via the gateway system when submitting electronic study data or described in the XML message of the eCTD. Since information entered in the analysis type are used to identify files on clinical pharmacology when creating the "Explanation of electronic study data package on clinical pharmacology", the analysis type should be appropriately entered.

In case of submissions using the PMDA window due to inevitable reasons, TSV files may be submitted, except for when referencing electronic study data from the XML message of the eCTD.

Information used to create the "Explanation of electronic study data package on clinical pharmacology" by the PMDA is as follows:

- Study ID: Letter sets identifying each study
- File path: A file path from the m5 folder, from which information on the file name is also obtained. In case of submissions of electronic study data using the gateway system, entering the file path is not necessary, except for when referencing electronic study data from the XML message of the eCTD because the gateway system imports the file path automatically.

- Analysis type: Type of analysis performed [Enter STS (standard pharmacokinetic analysis), POP (population analysis), PBPK (physiologically based pharmacokinetic model analysis), or Other (other than the above) using abbreviation]. For clinical study data that are not electronic study data on clinical pharmacology (refer to Attachment 1), enter Non-CP for all files. STS includes pharmacokinetic/pharmacodynamic analysis performed by the same method as for standard pharmacokinetic analysis. Enter Other for clinical pharmacology studies or analyses that are not STS, POP, or PBPK.
- Description: Explanation of the file content, which is used when STS, POP, PBPK, or Other is designated for the analysis type. Details need to be described specifying the use of each file and its relationship to other files. Description should be 100 characters or less.

4.2.2 Specific content of electronic study data to be submitted

Matters that must be followed with respect to standard pharmacokinetic analysis, population analysis, and physiologically based pharmacokinetic model analysis are shown below.

When submitting electronic study data on clinical pharmacology analyses that conform to the CDISC standards, please refer to 4.1. However, even in this case, please refer to 4.2.2.1 (3) for the analysis specifications on pharmacokinetics or pharmacokinetics/pharmacodynamics and information to be submitted in accordance with these specifications.

4.2.2.1 Standard pharmacokinetic analysis

Details in the case where analysis datasets are submitted in a format other than ADaM for the submission of electronic study data on standard pharmacokinetic analysis are as follows:

(1) Analysis datasets

Both analysis datasets for calculating PK or PD parameters and analysis datasets for statistical analysis using calculated PK or PD parameters (excluding the case where only summary statistics of parameters are derived) should be submitted. The file format should be as shown below, but an optional file format other than the followings is acceptable:

- SAS XPORT format (*.xpt)
- ASCII Format Data Files
- Phoenix Projects (*.phxproj)
- WinNonlin Files (*.pmo, *.pwo)

(2) Dataset definition documents

- The dataset definition document should include at least the variable names and the explanation of the variables and must be created by referring to Attachment 4. If the definitions are provided in the analysis result report, it would be sufficient to mention this fact and clearly state the relevant page number in the analysis result report.
- The file format, in principle, should preferably be a PDF, as specified in the eCTD v4 notification.

(3) Analysis specifications on pharmacokinetics or pharmacokinetics/pharmacodynamics and information to be submitted in accordance with these specifications

- This will include detailed information on the analyses that were performed, such as the analysis algorithms (for example, the method used to calculate the pharmacokinetic parameters) and the handling of

data below the lower limit of quantitation. If this information is included in the analysis dataset itself, it would be sufficient as long as this is stated clearly. If this information is included in documents such as the analysis plan, it would be sufficient to just submit these documents.

- The file format is optional.

4.2.2.2 Population analysis (including simulations)

Details for the submission of electronic study data on population analysis are as follows:

(1) Analysis dataset

Analysis dataset, which is finally used for model building of base model and final model, etc., and corresponds to program files for the model, should be submitted. The file format should be as shown below, but an optional file format other than the followings is acceptable:

- SAS XPORT format (*.xpt)
- ASCII Format Data Files

(2) Dataset definition documents

Refer to 4.2.2.1(2)

(3) Program files

Program files for analysis using base model and final model, etc., should be submitted. The file format should be as shown below, but an optional file format other than the followings is acceptable:

- ASCII Format Data Files

(4) Files into which major results are outputted

Output files including the analysis output using base model and final model, etc., (such as NONMEM output) should be submitted. The file format is optional.

(5) Files related to simulation

If the simulation results are used for decision-making, such as selection of patients to treat and setting of the dosage and administration, files related to the simulation should be submitted. The simulation results in this case include results on model-based posterior estimates, such as posterior estimates of exposure-related parameters (AUC, Cmax, etc.).

As files related to the simulation, program files for generating simulation data, performing simulation and making figures and tables showing simulation results etc. should be submitted. Submission of files related to a simulation performed for model evaluation (such as visual predictive check) and datasets created in the course of simulation is not mandatory. If a dataset, etc. related to existing information is used in the simulation, the dataset, etc. including such information, should be submitted. If it is difficult to submit those programs, the submission of specifications that show the analysis algorithm would be sufficient. The file format of programs is optional.

(6) Program procedures

Please describes the detailed procedures of running the program. It must include at least the program file names and the explanation of the programs and must be created by referring to Attachment 5. If it is not necessary to perform special processes, such as designating the path name, to use the submitted program, basically, the submission of program procedures is not necessary.

4.2.2.3 Physiologically based pharmacokinetic model analysis (including simulations)

Details for the submission of electronic study data on physiologically-based pharmacokinetic model analysis are as follows:

(1) Files that contain information on the model structure used for the analysis, the set values of drug and physiological parameters, analysis results, and sensitivity analyses

The file format is optional.

(2) Clinical study datasets, including blood concentration data

If the datasets were created or modified to be analyzed using a specific software for PBPK model analysis, the electronic files of the created or modified datasets should be submitted in the format for the specific software [Simcyp PE Data Files (xml format), etc.]. If the datasets were not created or modified for a specific software for PBPK model analysis, the datasets can be submitted in an optional file format. When submitting clinical study datasets, including blood concentration data, dataset definition documents should be submitted [refer to 4.2.2.1 (2)] as needed.

5. Relationship between electronic study data and eCTD for new drug applications

5.1 Relationship between electronic study data and eCTD

In principle, all electronic study data should be referenced from the XML message of the eCTD. Except for when referencing electronic study data from the XML message of the eCTD, information or files related to electronic study data should not be included in the XML message of the eCTD or the eCTD folder structure. However, whether or not electronic study data is being submitted must still be described, per study report, in the list of attachments in Module1.

5.2 Obtaining the eCTD receipt number from the gateway system

When submitting the eCTD, the applicant must enter the scheduled date of submission and necessary information beforehand and obtain the eCTD receipt number from the gateway system. Some examples of necessary information are as follows:

- Brand name of the product subject to application
- Application category
- New application/application for minor change
- Original/reference
- Scheduled submission date

5.3 Submission of the eCTD via the gateway system

When submitting the eCTD, the applicant must register, select, or enter administrative information on the gateway system. Some examples of administrative information are as follows. Not all items need to be registered, selected, or entered at each submission.

- Original/reference/replacement
- Gateway receipt number
- eCTD receipt number
- Submission sequence number
- Form (code)
- Application category
- Generic name of the product
- Brand name of the product

- Statement concerning virus check
- Checksum value of XML instance (XML message of the eCTD)
- Execution check environment
- Contacts for the regulatory affairs manager and eCTD technical manager
- Remarks

After registering, selecting, or entering the abovementioned details, please register the top level folder of the eCTD to be submitted on the gateway system and send it to the PMDA. For the details on operating the gateway system, please refer to the operation manual for the gateway system.

5.4 Receipt of the eCTD submitted via the gateway system

The PMDA will perform a virus check and validation of the eCTD and notify the applicant of the results together with the assessment on the acceptance of the eCTD. For the content of validation performed on the eCTD, in principle, please refer to the operation manuals of the eCTD verification tool published on the PMDA's website.

5.5 Relationship of the eCTD life cycle and electronic study data

Because electronic study data is part of the document to be appended to the application form, when changing (adding, replacing or deleting) electronic study data, it is appropriate to revise the eCTD. Except for when referencing electronic study data from the XML message of the eCTD, submission of administrative information related to electronic study data (as shown in 3.3) enables the identification of the eCTD related to this electronic study data. The applicant should consider the following points when submitting electronic study data.

(1) Electronic study data submitted upon the initial submission of the eCTD

After submitting electronic study data for the initial submission, once the PMDA notifies the acceptance of electronic study data, it is not possible to submit additional electronic study data related to the initial submission.

(2) Electronic study data submitted during the revision of the eCTD

- Only submit the difference with the previously submitted datasets. It is not necessary to resubmit electronic study data submitted with the previous submission sequence number.
- If there is no eCTD to be submitted with electronic study data, an applicant should consult the PMDA beforehand on the method of submission.
- Once the PMDA notifies the acceptance of electronic study data, it is not possible to submit additional electronic study data related to this submission sequence number.
- When submitting electronic study data after the committee on drugs, please follow the procedures in this section.

5.6 Change request during the submission of electronic study data

When submitting electronic study data during the revision of the eCTD, it is not necessary to submit the change request shown in Appendix 6 of "Confirmation of the Progress Status of New Drug Review" (PMDA Notification No. 1227001, by the Chief Executive of Pharmaceuticals and Medical Devices Agency, dated December 27, 2010).

6. Others

For products that require the submission of electronic study data but do not necessarily require the attachment to a new drug application to be a CTD, such attachments to the new drug application may be submitted electronically by the method specified in 3. In such a case, the standard electronic specification of the attachments to the new drug application will be provided separately.

Provisional Translation (as of June 2022)
Attachment 1

System of terminology used in this guide

- Electronic files (all files to be submitted via the gateway system)
  - Electronic study data for application (= electronic study data)
    - Clinical study data
      - [Clinical study data that exclude electronic study data on clinical pharmacology]
        - CDISC-conformant data (= data conformant to CDISC standards)
          - Dataset (= dataset for submission)
            - SDTM dataset (= dataset according to SDTM)
            - Analysis dataset (= ADaM dataset = dataset according to ADaM)
          - Definition file (= define.xml)
        - Legacy data
          - Dataset
          - Definition file
        - Program file
          - Program for analysis
          - Program for creating datasets
      - [Electronic study data on clinical pharmacology] (electronic study data on clinical studies where standard pharmacokinetic analysis was performed, population analysis, and physiologically-based pharmacokinetic model analysis)
        - CDISC-conformant dataset (= data conformant to CDISC standards)
          - Dataset (= dataset for submission)
            - SDTM dataset (= dataset according to SDTM)
            - Analysis dataset (= ADaM dataset = dataset according to ADaM)
          - Definition file (= define.xml)
        - Data in a format other than CDISC standards (= data when submitting analysis dataset in a format other than ADaM)
          - Dataset (= dataset for submission)
            - Analysis dataset (= dataset in a format other than ADaM)
            - Datasets other than analysis dataset (information on pharmacokinetic and physiological parameter values set in the physiologically-based pharmacokinetic model analysis)
          - Dataset definition document
          - Files into which major results were outputted
          - Files on simulations
          - Program procedure
        - Analysis specification (or documents containing comparable information)
        - Program file
          - Program for analysis
          - Program for creating datasets
        - Explanation of electronic study data package on clinical pharmacology
    - Documents to be appended
      - aCRF (Annotated CRF)
      - Reviewer's guide
        - SDRG
        - ADRG
  - eCTD (excluding electronic study data*)
  - FD application data
  - [Other data to be submitted via the gateway system]

* It may be called “eCTD” including electronic study data

Provisional Translation (as of June 2022)
Attachment 2

Examples of variables which may contain Japanese text

Domain Prefix	Variable Name	Variable Label	Type	CDISC Notes (for domains) Description (for General Classes)	Core
Common	--REASND	Reason Not Done	Char	Reason not done. Used in conjunction with --STAT when value is NOT DONE.	
Common	--RELNST	Relationship to Non-Study Treatment	Char	An opinion as to whether the event may have been due to a treatment other than study drug. Example: "MORE LIKELY RELATED TO ASPIRIN USE."	
DM	INVNAM	Investigator Name	Char	Name of the investigator for a site.	Perm
CO	COVAL	Comment	Char	The text of the comment. Text over 200 characters can be added to additional columns COVAL1-COVALn.	Req
SE	SEUPDES	Description of Unplanned Element	Char	Description of what happened to the subject during this unplanned Element. Used only if ETCD has the value of “UNPLAN”.	Perm
SV	SVUPDES	Description of Unplanned Visit	Char	Description of what happened to the subject during an unplanned visit.	Perm
CM	CMTRT	Reported Name of Drug, Med, or Therapy	Char	Verbatim medication name that is either pre-printed or collected on a CRF.	Req
CM	CMMODIFY	Modified Reported Name	Char	If CMTRT is modified to facilitate coding, then CMMODIFY will contain the modified text.	Perm
CM	CMINDC	Indication	Char	Denotes why a medication was taken or administered. Examples: NAUSEA, HYPERTENSION.	Perm
EX	EXADJ	Reason for Dose Adjustment	Char	Describes reason or explanation of why a dose is adjusted.	Perm
SU	SUTRT	Reported Name of Substance	Char	Substance name. Examples: Cigarettes, Coffee.	Req
SU	SUMODIFY	Modified Substance Name	Char	If SUTRT is modified, then the modified text is placed here.	Perm
SU	SUDOSTXT	Substance Use Consumption Text	Char	Substance use consumption amounts or a range of consumption information collected in text form.	Perm
AE	AETERM	Reported Term for the Adverse Event	Char	Verbatim name of the event.	Req
AE	AEMODIFY	Modified Reported Term	Char	If AETERM is modified to facilitate coding, then AEMODIFY will contain the modified text.	Perm
AE	AEACNOTH	Other Action Taken	Char	Describes other actions taken as a result of the event that are unrelated to dose adjustments of study treatment. Usually reported as free text. Example: “TREATMENT UNBLINDED. PRIMARY CARE PHYSICIAN NOTIFIED.”	Perm
DS	DSTERM	Reported Term for the Disposition Event	Char	Verbatim name of the event or protocol milestone. Some terms in DSTERM will match DSDECOD, but others, such as “Subject moved” will map to controlled terminology in DSDECOD, such as “LOST TO FOLLOW-UP.”	Req
MH	MHTERM	Reported Term for the Medical History	Char	Verbatim or preprinted CRF term for the medical condition or event.	Req
DV	DVTERM	Protocol Deviation Term	Char	Verbatim name of the protocol deviation criterion. Example: IVRS PROCESS DEVIATION - NO DOSE CALL PERFORMED. The DVTERM values will map to the controlled terminology in DVDECOD, such as TREATMENT DEVIATION.	Req

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Domain Prefix	Variable Name	Variable Label	Type	CDISC Notes (for domains) Description (for General Classes)	Core
PE	PEORRES	Verbatim Examination Finding	Char	Text description of any abnormal findings. If the examination was completed and there were no abnormal findings, the value should be NORMAL. If the examination was not performed on a particular body system, or at the subject level, then the value should be null, and NOT DONE should appear in PESTAT.	Exp
QS	QSTEST	Question Name	Char	Verbatim name of the question or group of questions used to obtain the measurement or finding. The value in QSTEST cannot be longer than 40 characters.	Req

(Reference: SDTM Ver.1.2, SDTM IG Ver.3.1.2, and later versions; descriptions have been partially omitted.)

Provisional Translation (as of June 2022)
Attachment 3

Sample methods for storing Japanese data

Example 1) Storing the verbatim term in Japanese without translating it into English
AE domain (alphanumeric dataset)

- For text items for which data was collected in Japanese, store the English character sequence (such as "JAPANESE TEXT IN SOURCE DATABASE") (collect AETERM in Japanese).

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESTDTC	AEENDTC	AEMODIFY	AEDECOD
1	ABC123	AE	123101	1	*JAPANESE TEXT IN SOURCE DATABASE*	2005-10-12	2005-10-12		Headache
2	ABC123	AE	123101	2	*JAPANESE TEXT IN SOURCE DATABASE*	2005-10-13T13:05	2005-10-13T19:00		Back pain
3	ABC123	AE	123101	3	*JAPANESE TEXT IN SOURCE DATABASE*	2005-10-21			Pulmonary embolism

Row	AEBODSYS	AESEV	AESER	AEACN	AEREL
1 (cont)	Nervous system disorders	SEVERE	N	NOT APPLICABLE	DEFINITELY NOT RELATED
2 (cont)	Musculoskeletal and connective tissue disorders	MODERATE	N	DOSE REDUCED	PROBABLY RELATED
3 (cont)	Vascular disorders	MODERATE	Y	DOSE REDUCED	PROBABLY NOT RELATED

Row	AEOUT	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDY	AEENDY	AEENRF
1 (cont)	RECOVERED/RESOLVED							-1	-1	
2 (cont)	RECOVERED/RESOLVED							1	1	
3 (cont)	RECOVERING/RESOLVING				Y	Y		9		AFTER

AE domain (Japanese dataset)

- For text items for which data was collected in Japanese, store them in Japanese without translating.

Row	STUDYID	DOMAIN	USUBJID	AESEQ	AETERM	AESTDTC	AEENDTC	AEMODIFY	AEDECOD
1	ABC123	AE	123101	1	*頭痛*	2005-10-12	2005-10-12		Headache
2	ABC123	AE	123101	2	*背部痛*	2005-10-13T13:05	2005-10-13T19:00		Back pain
3	ABC123	AE	123101	3	*肺塞栓*	2005-10-21			Pulmonary embolism

Row	AEBODSYS	AESEV	AESER	AEACN	AEREL
1 (cont)	Nervous system disorders	SEVERE	N	NOT APPLICABLE	DEFINITELY NOT RELATED
2 (cont)	Musculoskeletal and connective tissue disorders	MODERATE	N	DOSE REDUCED	PROBABLY RELATED
3 (cont)	Vascular disorders	MODERATE	Y	DOSE REDUCED	PROBABLY NOT RELATED

Row	AEOUT	AESCONG	AESDISAB	AESDTH	AESHOSP	AESLIFE	AESMIE	AESTDY	AEENDY	AEENRF
1 (cont)	RECOVERED/RESOLVED							-1	-1	
2 (cont)	RECOVERED/RESOLVED							1	1	
3 (cont)	RECOVERING/RESOLVING				Y	Y		9		AFTER

Example 2) If translation of the original text into English is difficult and the English character sequence needs to be distinguished from one another
QS domain (alphanumeric dataset)

Row	STUDYID	DOMAIN	USUBJID	QSSEQ	QSTESTCD	QSTEST
1	ABC123	QS	123101	1	QSTEST1	JAPANESE TEXT IN SOURCE DATABASE01
2	ABC123	QS	123101	2	QSTEST2	JAPANESE TEXT IN SOURCE DATABASE02
3	ABC123	QS	123101	3	QSTEST3	JAPANESE TEXT IN SOURCE DATABASE03

QS domain (Japanese dataset)

Row	STUDYID	DOMAIN	USUBJID	QSSEQ	QSTESTCD	QSTEST
1	ABC123	QS	123101	1	QSTEST1	*自分で布団を敷けますか？*
2	ABC123	QS	123101	2	QSTEST2	*ぞうきんがけはできますか？*
3	ABC123	QS	123101	3	QSTEST3	*ラジオ体操をしても平気ですか？*

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Provisional Translation (as of June 2022)

Attachment 4

(Reference) Dataset definition file

Dataset: XXXXX ("XXXXX" is the dataset name)

No.	Variable [*1]	Description [*2]
1	ID	Unique subject identifier
2	STUDYID	Study number
3	TIME	Time of the event relative to the first dosing of the study drug
4	AMT	Amount of drug administered
5	DV	Plasma concentration
6	CMT	Number of the compartment where the parameter was measured 1 = Dosing 2 = Parent drug 3 = Metabolite
7	MDV	Missing dependent variable data item for DV 0 = Valid PK measurement 1 = Other (missing or invalid value, dosing event, start of urine sampling)
X	XXXX	••••••

*1: Provide the variable name.

*2: Provide the description of the variable.

Provisional Translation (as of June 2022)
Attachment 5

(Reference) Program procedure

No.	Program file name [*1]	Description [*2]
1	xxxxxx	Software used: ○○ Ver.● Purpose: Used for ••••. Considerations for use: • Designate the folder to output the file with the following line. xxxxx <- “path name” • • Designate the folder to store the data file of •••• with the following line. xxxxx<- “path name” • Run the program up to the following line. ExportData(XXXXX) • Perform the •••• file (xxxxxx) for simulation on the CSV file (“xxxx”) outputted into a designated folder (xxxxx). • Store the output file (xxxxx) to the folder (xxxxx) designated above. • Resume the program from the line below, then import and analyze the stored output file (xxxxx). xxxxx <- importData(XXXXX)
X	xxxxxx	Software used: ○○ Ver.● Purpose: Used for ••••. Considerations for use: ••••

*1: Provide the file name of the program.

*2: Provide the description (such as the software used, purpose, considerations for use) of the program.