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Single Day Event

Sharing Survey Result of eData Submission for Real World Data, and Reduction of CSR Listing from PHUSE Japan eData Submission Working Group

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Disclaimer

The contents of this presentation represent the opinions of the PHUSE Japan eData submission working group / individual presenters and do not represent the opinions or positions of the organization to which they belong.

Declaration

Since this survey required to enter the information of the company name, etc., all PHUSE Japan eData submission working group members who have access to the survey results can obtain confidential information in all responding companies , but we hereby declare that we will NOT use it for unintended purposes.

Outline

1. Survey result of reduction of CSR listing
2. Survey result of eData submission for real world data

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1. Survey result of reduction of CSR listing
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Data Listings in Clinical Study Reports published by PHUSE Safety Analytics Working Group

PHUSE Safety Analytics Working Group (23-Nov-2021), Data Listings in Clinical Study Reports, WP061.pdf

The purpose of this white paper is to provide recommendations and justification for listings to include (and not include) in eCTD CSR Sections 14 and 16 and regulatory submissions, with example alternatives to static listings. Since the listings in CSR Section 14 are narrower in scope, the focus is mainly on general study data listings in Section 16.*

* Static listing – A listing that is created without any interactive features, to be viewed in its entirety on one or more pages. An example of a static listing would be an RTF or PDF file displaying data collected for a study. The file may be viewed, but no other interaction is possible.

Data Listings in Clinical Study Reports published by PHUSE Safety Analytics Working Group

Background

The below listings from the PHUSE CSS Survey may also be useful for review

1. Facilitates identification of subjects
2. Provide sufficient information to discuss results in the CSR

Deaths	Adverse Events Related to Study Treatment
Serious Adverse Events	Demographics/Baseline Characteristics
Adverse Events Leading to Study Treatment Discontinuation	Markedly Abnormal Clinical Laboratory Values
Study Withdrawals	Randomization
Protocol Deviations	Study Medication Lot Numbers by Subject
Adverse Events of Special Interest	Primary Efficacy Parameters

Recommendation

- **Stop routinely creating all static listings**
- For each regulatory authority
  - EMA: According to the guidance, “protocol deviations ” and“ serious adverse events ” should be included in only two CSRs.
  - **The FDA/PMDA/NMPA: Receives electronic data and has review tools**
- **Static listings are an inefficient method for review, so when creating SDTM/ADaM datasets instead, it is recommended to use SDTM/ADaM for reviewing the data.**
- Static listings may be created for internal use, etc.

Overview of Survey result of Reduction of CSR Listing

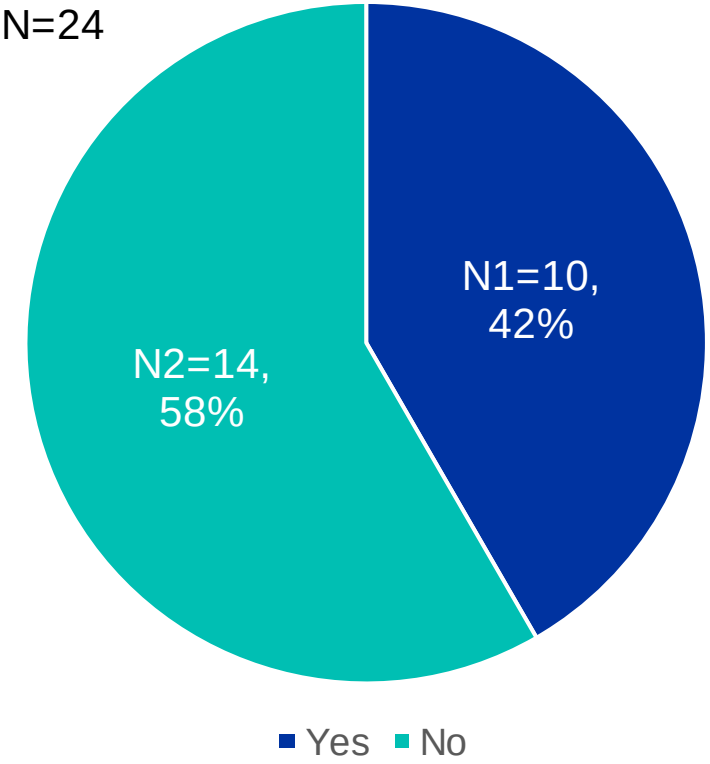
Activities	Our sub team in the PHUSE Japan eData submission WG is working to collect information about CSR listing based on this paper (**WP061.pdf**).
Purpose	To understand the current status of initiatives to reduce CSR listings among Pharmaceutical companies.
Duration	30Sep – 11Oct in 2024
Contents	• Status of CSR listing reduction in (global/domestic) pharmaceutical companies in Japan • General consideration of reduction in CSR listing
Target respondent	Member companies of PHUSE & CDISC Japan User Group ADaM team (limited to companies operating in Japan) One response per one company
Number of response	24

Please describe how CSR Listings have helped your company.

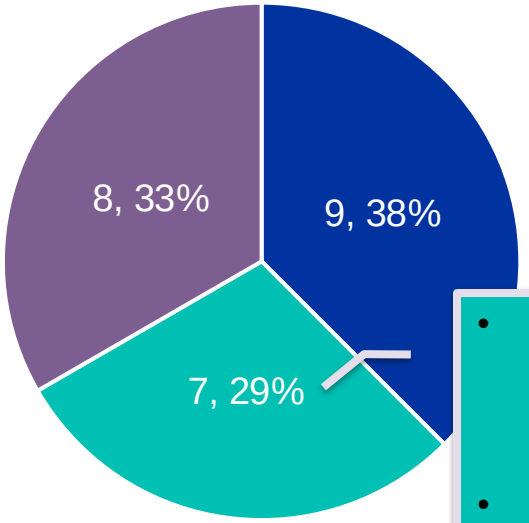
- It is helpful for persons who cannot directly access SDTM/ADaM dataset such as MW when preparing CSR to review the data. However, SDTM/ADaM dataset may be provided separately using Excel, etc.
- The PMDA confirms data consistency (whether the contents of the CRF, and/or the derivation on data handling, etc. are appropriately reflected in the CSR) during the inspection.
- The listings are referred for a specific case to prepare for the inspection.
- Listings may be viewed for old studies without available eData.

Do you have any experiences submitting a CSR with listing reduction to the PMDA?

N=24



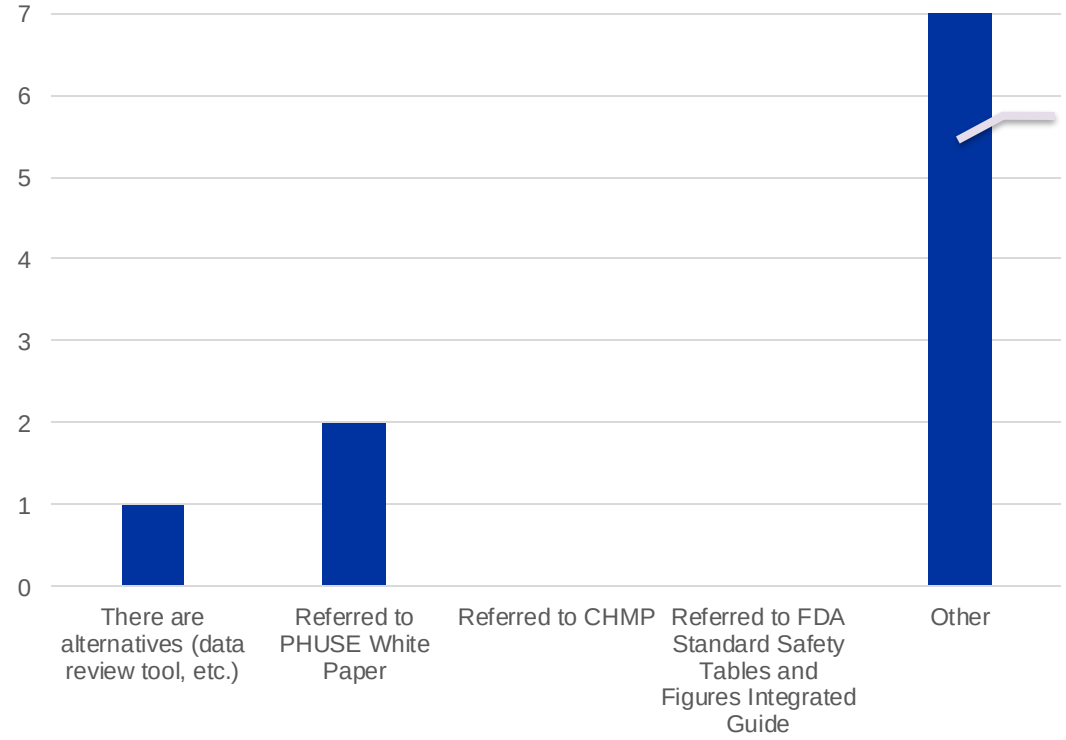
To what extent do you create CSR listings in your regular analysis work?



- One company: Create partial listings in global study, but create all listings in Japanese Phase I study
- Not create Inclusion/Exclusion criteria, Kit number

Please select the reasons/rationales for the CSR listing reduction (multiple selections possible). If there are other reasons/rationales, please select "Other" and provide details.

N1=10 No company selected more than one.

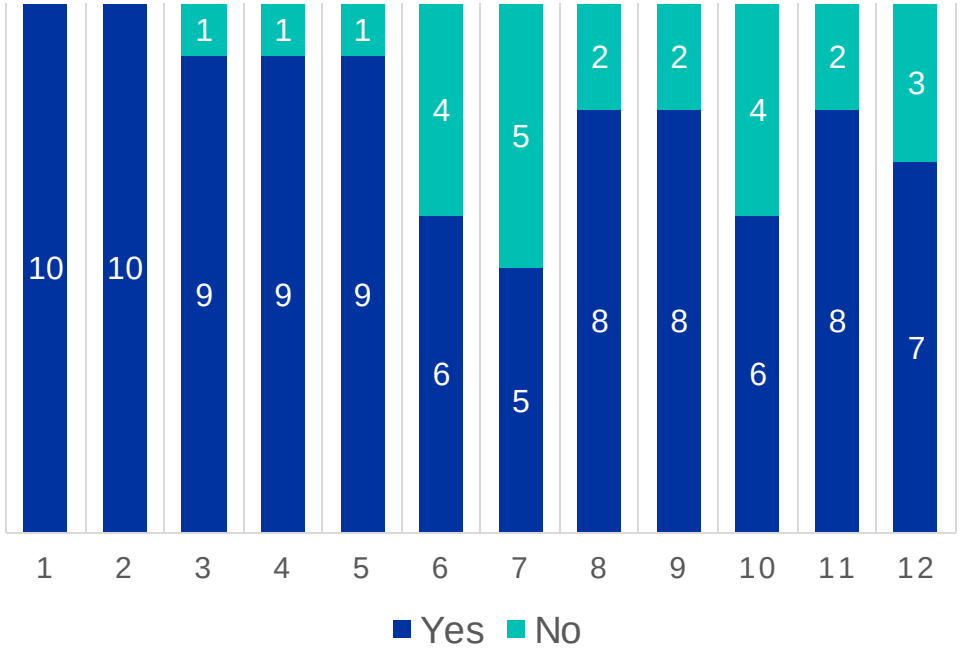


Reason for "Other"

- Almost of the company follow their own policy.

Please answer whether you have prepared the 12 CSR Listings suggested in the PHUSE White Paper*

N1=10



*Reference:
Data Listings in Clinical Study Reports WP061.pdf

1. Deaths
2. Serious Adverse Event (SAE)
3. Study Withdrawals
4. Adverse Event Leading to Study Treatment Discontinuation
5. Protocol Deviations (PD)
6. Adverse Event of special Interest (AESI)
7. Adverse Event Related to Study Treatment
8. Demographics/Baseline Characteristics
9. Markedly Abnormal Clinical Laboratory Values
10. Randomization
11. Study Medication Lot Numbers by Subject
12. Primary Efficacy Parameters

Please provide any examples of listing reduction other than above, conditionally reduced listings, or any comments on listing reduction.

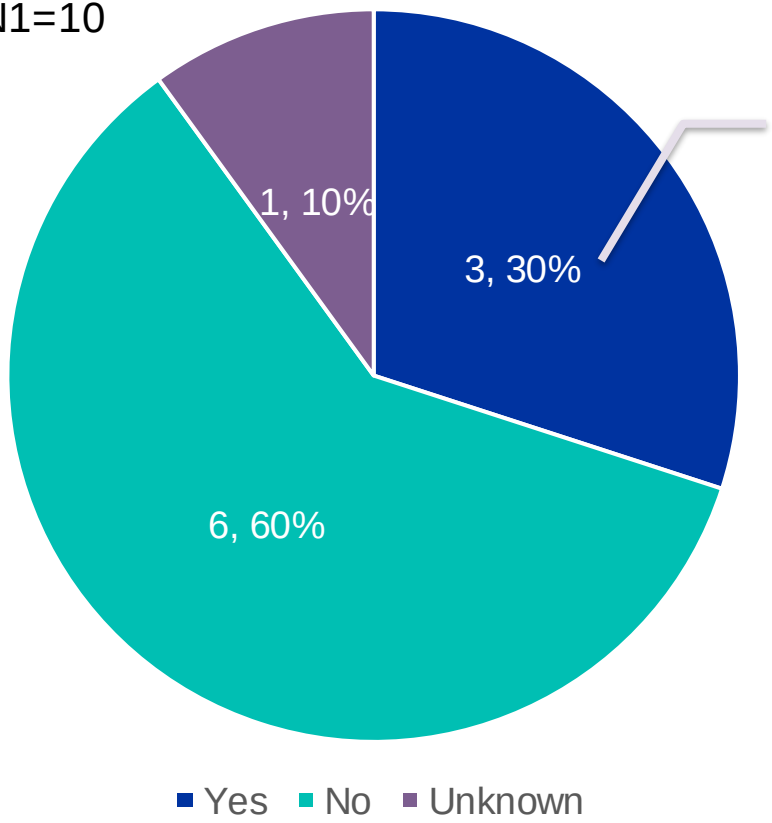
- Concomitant medication / Non-drug therapy is not created.
- Listing of Exposure, PK, Key efficacy parameter is recommended.
- All listings are not created when there are no death subjects in the study other than Oncology. Or patient narrative is referred when there are a few death subjects.
- All listings described in the PHUSE white paper (see slide 11) are created as per internal guidance, they may not be created depending on the phase or study description.
- Demographics/Baseline Characteristics is created when important item is included.
- In some cases, listing by type of AE (Related, AESI, etc.) is not created and only listing of all AEs is created.
- For the listing of deviations and subjects excluded from analysis specified in the ICH E3 Guideline, other documents were used.

Please describe any inconveniences or solutions within the company due to the reduction of CSR listings.

- By reducing the listings, inquiries from departments that want to refer to individual data such as MW increase, And also datasets (SDTM/ADaM) has to be provided to them.
  - Data Science Department supports other departments to see data using data review tool such as R/SAS JMP etc. However, they need to set up / manage the tool.
  - It cannot be used due to the CSV of the tool.
- It is difficult to take a consistent action for all studies because the necessity and importance of listing differ among disease areas and study sizes.
- Listings not generated in the CSR must additionally be generated for inspection.

Do you have any experiences to create additional Listings for CTD submitted to the PMDA due to CSR listing reduced?

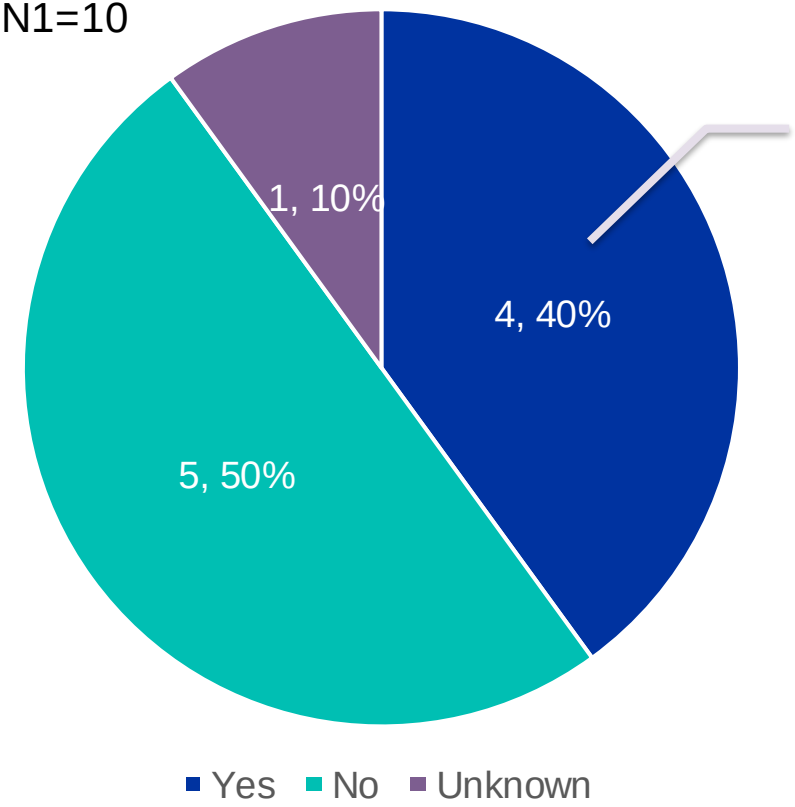
N1=10



- Markedly Abnormal Clinical Laboratory Values
- Listing attached on CTD M5.3.7 in case
- Listing of Deaths/SAE in Japanese (The CSR may create listing in English)

Do you have any experiences creating additional listings for the PMDA inspection?

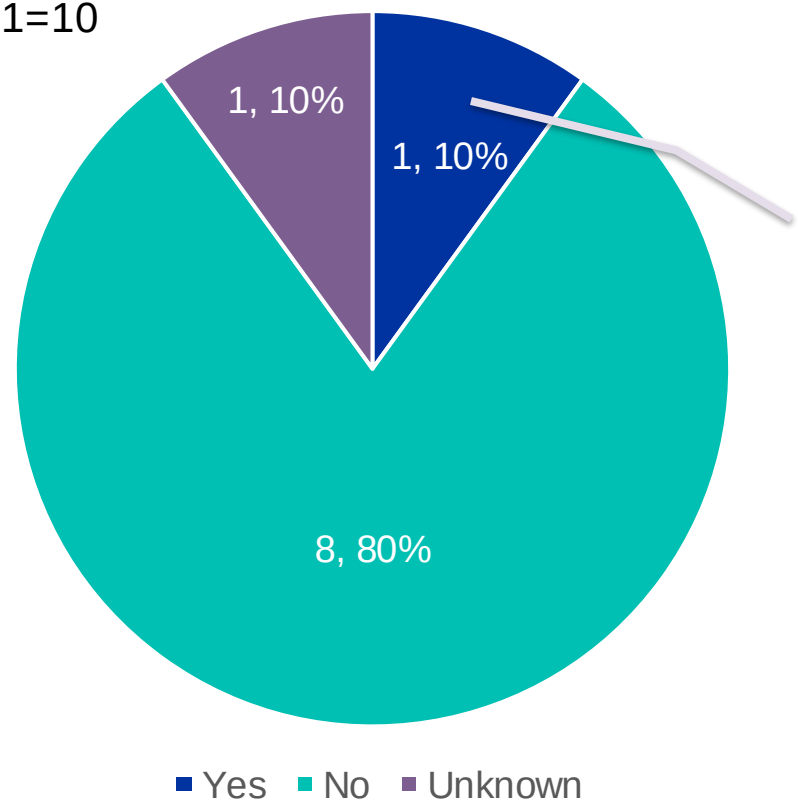
N1=10



- Listing of efficacy endpoint
- Listing of demographic
- Listing of QOL/concomitant medication/vital sign/laboratory which was not included in global study
- Listing in slide 11 which was not included in global study

Did the PMDA point out the reduced listings as inquiries or request additional actions?

N1=10



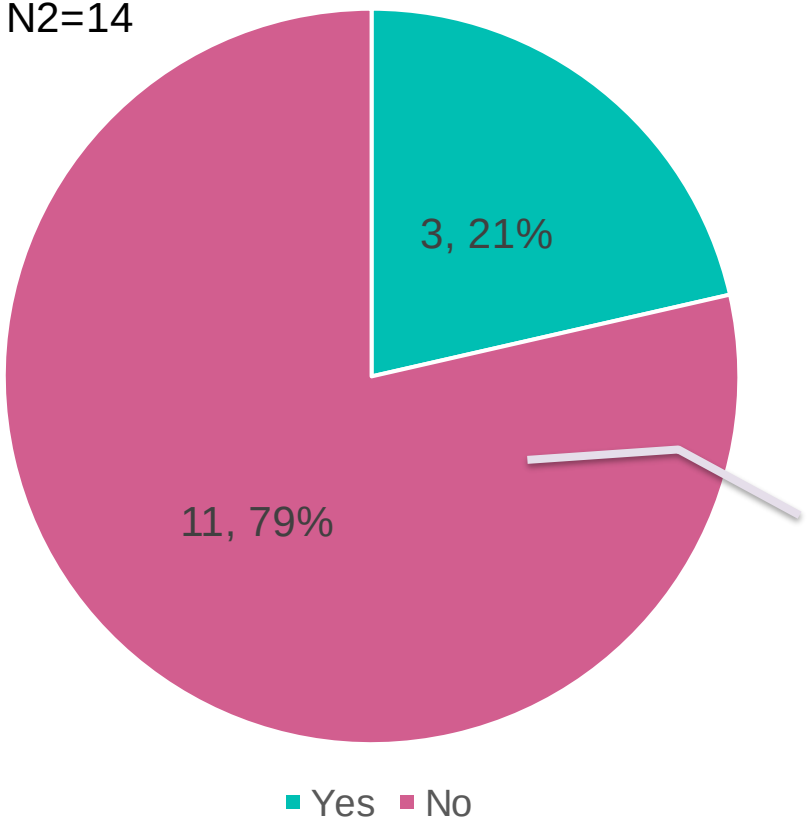
- Since a listing of information necessary for responding to inquiries was not prepared, excel data corresponding to the listing was prepared and provided in an additional analysis. For example, listing dosing records, concomitant medications, medical history/current medical conditions, weight, ECG

Have you consulted with the PMDA in advance about reducing the CSR listings? If yes, please describe the timing.

All companies do NOT consult with the PMDA in advance.

Do you have any plans to reduce CSR listings in the future?

N2=14



- It is unclear whether the PMDA will accept the CSR with reduced listing.
- To avoid potential delay in filing due to reduced listing.
- Policy cannot be changed unless it is understood by department utilizing the listing in the CSR.
- There is a certain hurdle for other departments (e.g. MW) to use SDTM/ADaM dataset instead of listing.

Please describe any issues or information you would like to know in order to reduce CSR listings in the future.

- Actual experience in other companies during the review period
  - Benefit-risk information, including whether or not an additional listing was actually requested by the PMDA during the review period
- How to coordinate with departments other than Data Science?
- Is the PMDA planning to issue any guideline?
  - Is it necessary to submit all listings in ICH E3?
  - Based on the guidelines, some companies can internally consider reducing CSR listing.

If you have any observations on the provision of listings to the PMDA, please note them here.

- Utilization of CSR listing and eData by the PMDA during review period including inspection
  - How much does the PMDA refer to eData and CSR listing?
  - Is there an opportunity for non-statistician to review SDTM data?
  - What is the purpose of the CSR listing?
  - When is the CSR listing used in the review process? (The CSR listing with pdf file seems to be difficult to use…)

Conclusion

Some companies are filing applications by using CSR listing reduced.

- CSR listing is created as per company policy.
- However, additional listing may be created in CTD and for inspection.

In reducing the CSR listing, Data Science department additionally provides other departments with SDTM/ADaM datasets, therefore there is a certain hurdle for reduction of CSR listing.

- Promote the introduction of tools, etc. that enable the departments that use the CSR listing to handle SDTM/ADaM data.

The impact on application cannot be understood by reducing CSR listing.

- Reduction of CSR listing is considered if the PMDA announces its policy for reducing the CSR listing, and/or if knowing how much the PMDA uses eData and CSR listing during the review period.

Outline

1. Survey result of reduction of CSR listing
2. Survey result of eData submission for real world data

eData submission for Real World Data

Activities	Our sub team in the PHUSE Japan eData submission WG is working to summarize the status of eData preparation using RWD and submission to PMDA in Japan.
Purpose	To summarize the current status of eData preparation using RWD and submission to PMDA in Japan.
Duration	30Sep – 11Oct in 2024

Contents	• Status of preparation and submission of eData using RWD to the PMDA
	  • "Japan New Drug Application (JNDA)"
	  • "Drug Re-examination Application (only for Post-marketing DB survey)"
	• General consideration of pharmaceutical companies in Japan on preparation of eData using RWD

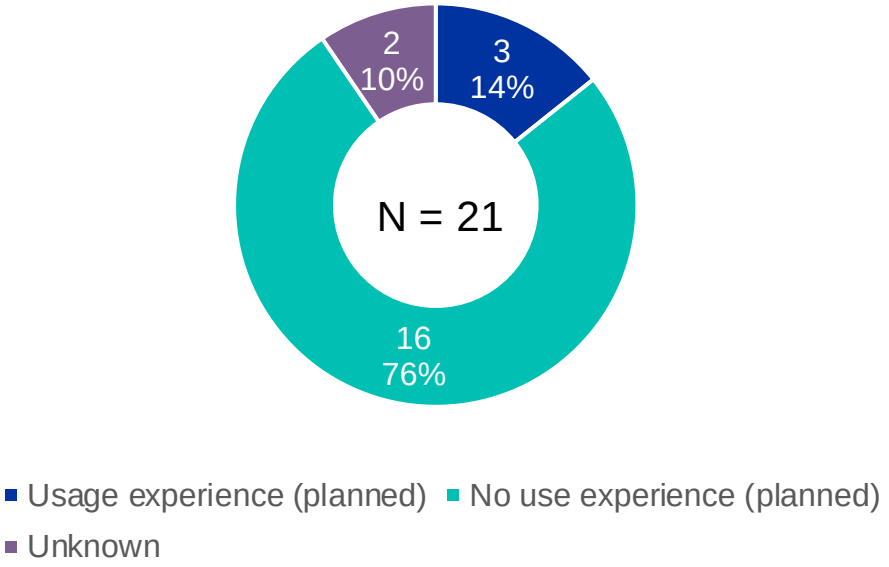
Target respondent	Member companies of PHUSE & CDISC Japan User Group ADaM team (limited to companies operating in Japan) One response per one company
Number of response	21 (Thank you for your cooperation!!)

Results of the survey

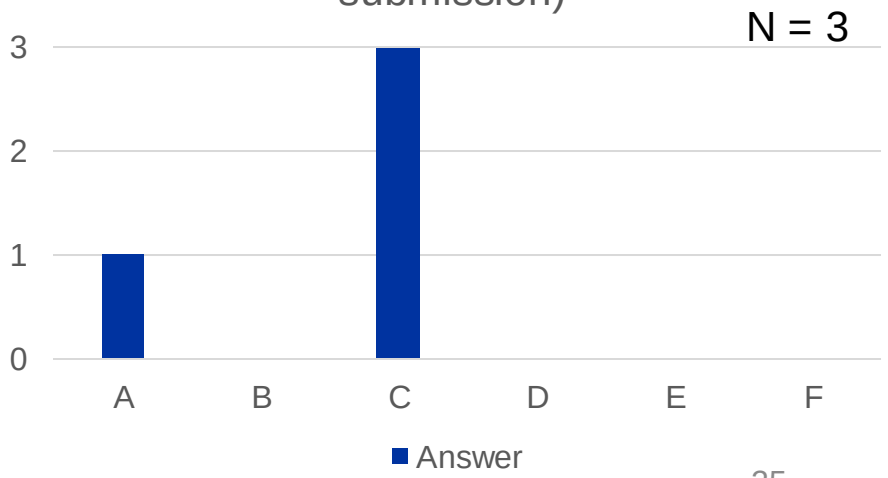
JNDA

A: Electronic Medical Record (EMR) data
B: Medical Claims and payments (claim) data
C: Drug and Disease Registry Data
D: Patient-generated data in daily life (data obtained from smartphones or wearable devices)
E: Data from other sources from which health status can be obtained, such as mobile devices
F: Other

Has RWD been used (or is there any plan to use) in Japan new drug applications? (Without regard to electronic data submission)



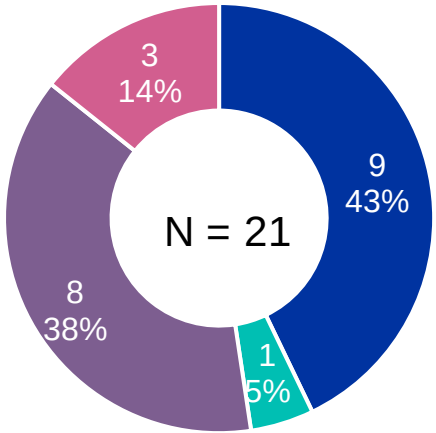
If "Usage experience (planned)" is selected, what type of RWD was used (if any)? (Without regard to electronic data submission)



Results of the survey

JNDA

Which department preparing electronic data submission for RWD application?
(Other: even if the department in charge of preparation differs in SDTM/ADaM)



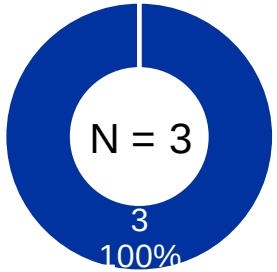
Other details
SDTM:Data Management ADaM:Statistician/ Statistical Programming
Value Evidence Outcome dept. and Statistical Programming
NA

Results of the survey

JNDA

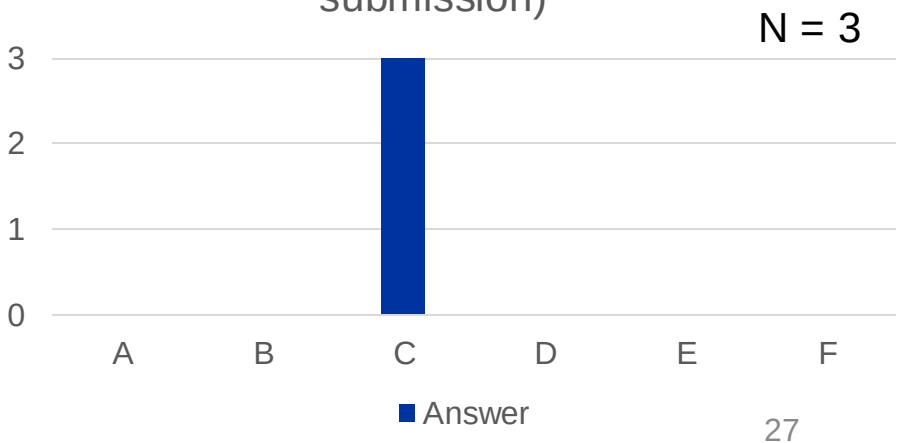
A: Electronic Medical Record (EMR) data
B: Medical Claims and payments (claim) data
C: Drug and Disease Registry Data
D: Patient-generated data in daily life (data obtained from smartphones or wearable devices)
E: Data from other sources from which health status can be obtained, such as mobile devices
F: Other

If "Usage experience (planned)" selected, status of electronic submission of RWD used for application (planned).



- Electronic data submission according to the CDISC standards (planned)
- Electronic data submission in a format not compliant with the CDISC standards (planned)
- Electronic data submission in both CDISC standard compliant and non-compliant formats (planned)
- No experience (plan) with electronic data submission

If "Electronic data submission according to the CDISC standards (planned)" is selected, what type of RWD was used (if any)? (Without regard to electronic data submission)

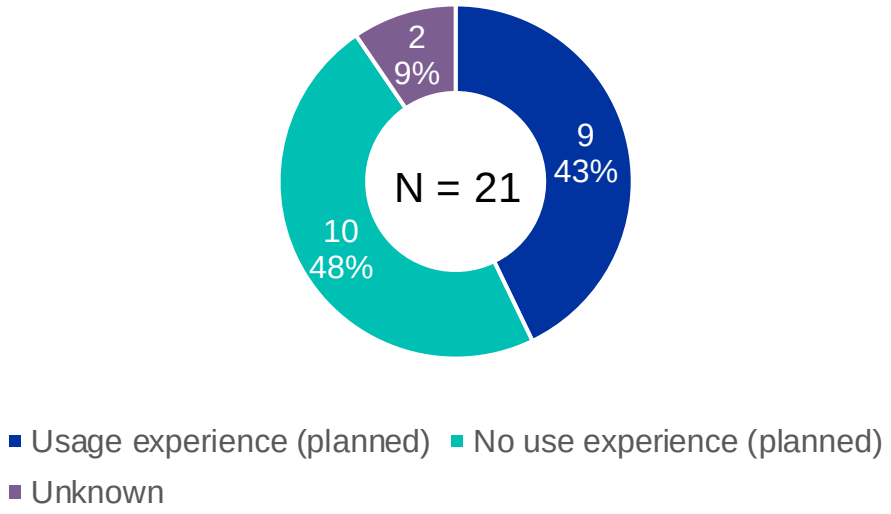


Results of the survey

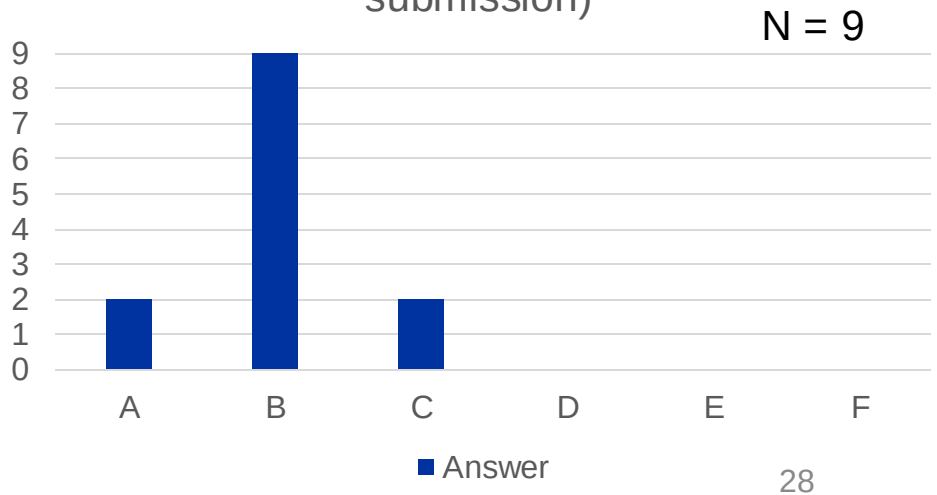
Drug Re-examination Application

A: Electronic Medical Record (EMR) data
B: Medical Claims and payments (claim) data
C: Drug and Disease Registry Data
D: Patient-generated data in daily life (data obtained from smartphones or wearable devices)
E: Data from other sources from which health status can be obtained, such as mobile devices
F: Other

Has RWD been used (or is there any plan to use RWD) in the application for re-examination?
(Without regard to electronic data submission)



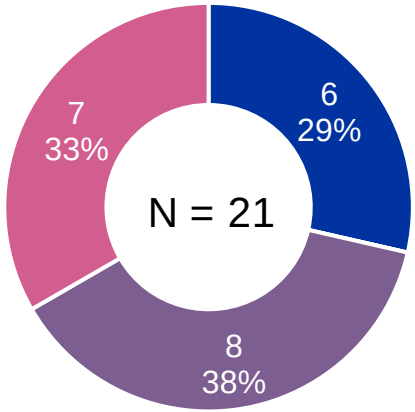
If "Usage experience (planned)" is selected, what type of RWD was used (if any)?
(Without regard to electronic data submission)



Results of the survey

Drug Re-examination Application

Which department preparing electronic data submission for RWD application?
(Other: even if the department in charge of preparation differs in SDTM/ADaM)



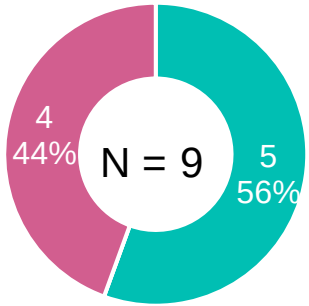
Other details
Post-marketing surveillance dept.
PV and Statistician/ Statistical Programmer
Statistical Programmer in PV dept.
PMS
CRO (Statistical dept.)
GPSP Planning dept.
NA

Results of the survey

Drug Re-examination Application

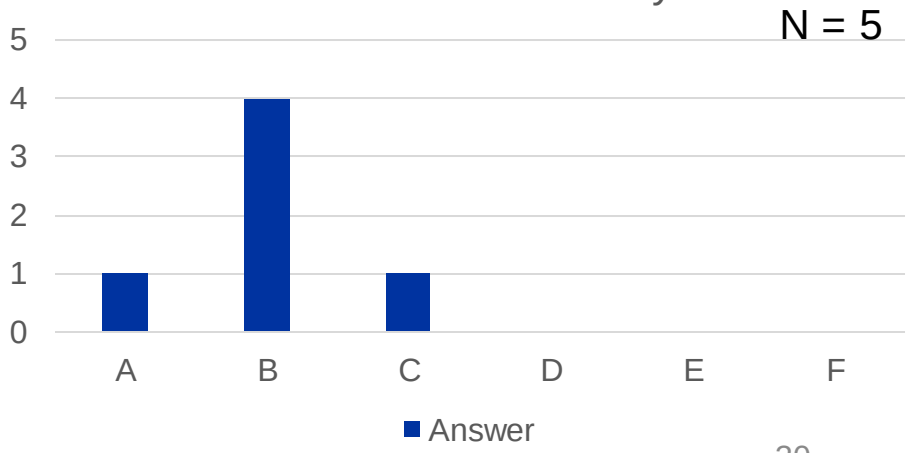
A: Electronic Medical Record (EMR) data
B: Medical Claims and payments (claim) data
C: Drug and Disease Registry Data
D: Patient-generated data in daily life (data obtained from smartphones or wearable devices)
E: Data from other sources from which health status can be obtained, such as mobile devices
F: Other

If "Usage experience (planned)" is selected, status of electronic submission of RWD used for application (planned).



- Electronic data submission according to the CDISC standards (planned)
- Electronic data submission in a format not compliant with the CDISC standards (planned)
- Electronic data submission in both CDISC standard compliant and non-compliant formats (planned)
- No experience (plan) with electronic data submission

If "Electronic data submission in a format not compliant with the CDISC standards (planned)" is selected, which type of RWD was (or will be) submitted electronically?



Results of the survey

Drug Re-examination Application

In CDISC standard non-compliant formats,
What deliverables were (or will be) submitted?

- Datasets received from DB vendor
  - Raw data extracting necessary cohorts/periods from receipt data
  - Analysis dataset converted from raw data

- Supplemental documents
  - Data specification (processable Excel file, etc.)
  - Information on datasets and variables used for analysis
  - Information showing conditions for identification from analysis datasets to identification of analysis populations

* Guidance for GPSP Compliance Inspection for Re-examination
https://www.jpma.or.jp/information/evaluation/results/allotment/lofurc000000v3fo-att/compatibility_Ver2.pdf

Results of the survey

General

How is the reliability of RWD to be used in the regulatory affairs at the time of application secured (Departments involved, methods, etc.)?

- Communication with DB vendor
  - Check the policy for explaining the reliability of RWD required by PMDA
  - Check the status of reliability assurance of RWD and the related procedures at DB vendors
  - For Drug Re-examination Application
    - Use Internal SOP “DB Vendor Checklist” (Based on MHLW notification: 000223003.pdf)
    - Use “DB survey management tools” (再審査申請時の調査（GPSP実地調査／適合性書面調査）｜独立行政法人 医薬品医療機器総合機構)
- Department involved
  - Dept. Leading the use/utilization of RWD
    - Data Manager, Programmer, Statistician, Data Science, Epidemiology, etc.
    - GPSP dept. (Drug Re-examination Application)
  - Quality Assurance

Results of the survey
General

Advantages of the use of the CDISC standards in the electronic submission of RWD applications

- Analysis activity Smoothly (difficulty level of usual clinical studies)
  - Easy for PMDA or person who are not familiar with RWD to understand
  - Possibility of fewer questions from PMDA
- Tools and systems developed and purchased for clinical studies are available
- Easy to integrate multiple RWDs/to perform cross-sectional analyses
  - Especially in rare diseases, it may be possible to apply for JNDA without conducting RCT, saving time and expenses

Results of the survey
General

Issues of the use of the CDISC standards in the electronic submission of RWD applications

- Limitations of Mapping to CDISC Standards (especially SDTM)
  - No standard for RWD
    - Handling of receipt data with different design principles from CDISC standards
    - Not collected data required for conversion to CDISC standards (Missing Req. Variables)
    - Controlled Terminology (Collected non-expandable code)
    - Translation of RWD collected with Japanese data
- Huge costs and resources to do the activity
  - Takes more time than legacy data conversion
- Too large data size
  - Original data cannot be converted to xpt format
  - Lack of PC Performance in Programming

Results of the survey
General

What tools and support are considered necessary when the CDISC standards are used for electronic data submission of RWD application

- Deregulation
  - Acceptance of Error/Reject issues or Establish validation rules for RWD
  - Acceptance in non-CDISC compliant data
- Establish cooperation system among DB vendor, pharmaceutical companies and PMDA
  - Direct communication between the DB vendor and PMDA at the time of inquiries and compliance inspections
- Enhanced notifications/tools
  - Guidance and tools to make representative receipt data convert to CDISC standards
  - Mapping table between Terms Used in RWD and CDISC (ICD10 vs MedDRA, Test Name vs NCI CT)
  - Notification clearly showing the data and the scope to be submitted at Drug Re-examination Application
- Standardization of a wide variety of RWD

Results of the survey
General

Creative measures taken / issues when communicating with database vendor (including academic societies) to prepare electronic RWD application data

- Cooperation between DB vendors and pharmaceutical companies
  - Follow-up of DB Vendors with insufficient experience of using DB under pharmaceutical regulations or communicating with PMDA
  - Preparation an evaluation tool to ensure reliability of DB
- Documentation of processes and definitions
  - Flow until data collected are used for analysis
  - Data extraction conditions used for analysis
- Consider the process of preparing TFLs from RWD
  - When preparing CDISC standard data, preparing TFLs from the CDISC data is efficient (It is difficult to confirm the reproducibility when customized analysis datasets are used)

Results of the survey
General

Opinion about submitting RWD at the time of application using the CDISC standard

- Risks of applying the CDISC standards outweigh the benefits
  - Risk of enormous costs, resources, and work time for converting non-standardized RWD (not planned to be standardized in the future) to CDISC standards or risk of difficulty in predicting them
  - Meaning of applying validation rules for clinical trial data to RWD
  - Need to show benefits to DB Vendor
- Consider that the analysis results based on RWD will be widely used including applications to regulatory authorities in other countries
  - Particularly for the receipt data, differences in the healthcare system among countries affect the characteristics of the DB
- Use of RWD for application is meaningful for us and should be promoted
  - Easer of regulations on eData submission will affect the promotion of the use of RWD at application

Conclusion

- Opportunities to use RWD for JNDA/Drug Re-examination Application is increasing
  - Especially, use of RWD in Drug Re-examination Application
  - Use of RWD for application is meaningful for us

- Conversion from RWD to CDISC standards is high challenging
  - Risk of enormous costs, resources, and work time for the conversion
  - Need to collaboration with stakeholders and to enhance notifications/tools
  - It is possibility that easer of regulations on eData submission will affect the promotion of the use of RWD at application
    - Acceptance of Error/Reject issues or Establish validation rules for RWD
    - Acceptance in non-CDISC compliant data

Sub team member

Reduction of CSR listing

- Takashi Kitahara (Novartis Pharma K.K.)
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- Iori Sakakibara (J&J)
- Kayo Inushima (Biogen)
- Keita Takahashi (Chugai)
- Takafumi Kamon (A2 Healthcare)
- Tomohiko Funai (Eli Lilly)
- Naoki Yoshida (Takeda Pharmaceutical Company Limited)
- Zhengyan Luo (Bristol-Myers Squibb)

eData submission for Real World Data

- Eri Sakai (Novartis Pharma K.K.)
- Iori Sakakibara (J&J)
- Rie Kageyama (Sumitomo Pharma Co., Ltd.)
- Ryo Watanabe (A2 Healthcare)
- Yasuhiko Ozawa (AstraZeneca)

Reference

Reduction of CSR listing

- PHUSE Safety Analytics Working Group. “Data Listings in Clinical Study Reports.” PHUSE WP-061, Version 1.0. 23 November 2021, WP061.pdf
- Mercidita Navarro, Genentech; Nancy Brucken, IQVIA; Aiming Yang, Merck & Co., Inc, “Just Say No to Data Listings!”, PharmaSUG 2022 - Paper SI-162, Just Say No to Data Listings!
- FDA, Standard Safety Tables and Figures: Integrated Guide, 08 February 2023, Regulations.gov

eData submission for Real World Data

- Data Standards for Drug and Biological Product Submissions Containing Real-World Data Guidance for Industry (December 2023) Data Standards for Drug and Biological Product Submissions Containing Real-World Data | FDA
- Guidance for GPSP Compliance Inspection for Re-examination (https://www.jpma.or.jp/information/evaluation/results/allotment/lofurc000000v3fo-att/compatibility_Ver2.pdf)
- Points to consider for ensuring reliability in post-marketing database surveys for drugs (000223003.pdf)
- DB survey management tools (再審査申請時の調査（GPSP実地調査／適合性書面調査） | 独立行政法人 医薬品医療機器総合機構)

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