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OPINION PAPER

Initiative for CDISC Standardization of Clinical Trial Data in Academia: The Experience of Tohoku University Hospital

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In Japanese academia, Clinical Data Interchange Standards Consortium (CDISC) standards have not progressed mainly due to resource issues. The Tohoku University Hospital Clinical Research Data Center has integrated these standards into operations since 2013. Our objective is to implement CDISC standards to enhance quality and efficiency, and to establish systems for Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) creation for electronic data submission. This paper describes our CDISC activities, focusing on experience and lessons learned in investigator-initiated clinical trials and registry studies through 2023. We assigned dedicated personnel to consolidate CDISC knowledge and manage outsourcing, facilitating implementation through Data Management, Biostatistics, and Medical Information Management collaboration. Work time decreased significantly after our first in-house implementation. Challenges were addressed via our Quality Management System, resulting in standardized CRF templates. We continue exploring optimal CDISC utilization from multiple group perspectives to standardize, streamline, and automate processes across our organization.

Keywords: clinical data interchange standards consortium (CDISC); academic research organization (ARO); electronic study data submissions; data sharing; quality management system (QMS); clinical data interchange standards consortium; CDISC; academic research organization; ARO; quality management system; QMS

Introduction

In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) began accepting electronic data submissions for clinical trials in accordance with the Clinical Data Interchange Standards Consortium (CDISC)[1] from October 2016. In April 2020, the submission of such data became mandatory.[2] The Japan Agency for Medical Research and Development (AMED) website states that future clinical research and clinical trials, even those led by academia, are expected to be required to comply with CDISC standards if commissioned by AMED.[3]

According to a survey conducted in 2020,[4] only 19.5% of Academic Research Organizations (AROs) in Japan have experience in creating or commissioning CDISC standard data; and 85.4% of the respondents said that the biggest obstacle to this was "lack of resources due to high human and financial costs". Since solving this lack is difficult, it is essential to consider how CDISC implementation can proceed under such circumstances.

The Tohoku University Hospital Clinical Research Data Center (hereafter the Data Center) is an ARO data center, comprising four groups (monitoring, data management, biostatistics, and medical information management). The Data Center provides support for investigator-led clinical trials and clinical research by assisting with research protocols and Case Report Forms (CRFs), establishing data collection systems, clinical data management, monitoring, and statistical analysis as an independent third party from the researchers. The Data Center also provides quality control and consultation to ensure reliable clinical research results.

The objectives of implementing the CDISC standards at our Data Center are:

1. To apply CDISC standards to operational processes for improving quality and efficiency.
2. To establish a system that uses the Study Data Tabulation Model (SDTM)[5] framework and Analysis Data Model (ADaM)[6] standards for electronic data submission during approval applications to accelerate the bridge to practical implementation.

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This paper focuses on our experience at the Data Center in implementing CDISC standards for investigator-initiated clinical trials and registry studies through 2023, and how operations were standardized and streamlined. The work at the Data Center faces barriers that include a lack of resources, and the diversity of sponsor requests and disease areas, and based on this, we present considerations from our experience at the Data Center.

Efforts to Standardize Data Center Operations by Applying CDISC Standards

Figure 1 shows our Data Center structure and CDISC roles: Data Management Group, creation of CRFs considering Clinical Data Acquisition Standards Harmonization (CDASH)[7] and SDTM, creation of SDTM; for Biostatistics Group, creation of ADaM; in Medical Information Management Group, one lead CDISC staff member is assigned to promote the introduction of CDISC and collect information.

Data Center started gathering information on CDISC initiatives in 2013, attending CDISC Japan Interchanges and seminars. And held CDISC study sessions in the Data Center (2014, 2015) and participated in official CDISC training.

In 2014, the Data Center created a standard CRF template in oncology. However, it was not widely used due to a combination of factors including diverse protocols, and the fact that when similar studies were conducted by the same client previously, they often based new CRFs on previous ones, rather than using the template. The "CRF creation support" procedure was therefore developed to integrate with existing CRF creation procedures. Before studies began, CDASH and SDTM variables were mapped to CRF input items, and conformance to CDASH and SDTM rules was checked, which prevented fatal data errors in the later SDTM and ADaM creation stages.

Since 2017, the Data Center has been reviewing its organization for ISO 9001:2015 certification to establish a quality management system (QMS), and has created a "Business Flow Diagram" that visualizes workflow and coordination among the group. The diagram includes CDISC standard-compliant tasks such as CRF creation support, SDTM, and ADaM creation, which clearly positions them as data center operations.

In 2022, the Data Center resumed the development of a standard CRF template to improve efficiency and to facilitate SDTM conversion. Using CDASH-compliant CRF templates from Electronic Data Capture (EDC) vendors, the Data Center created standard CRF templates that could be used partially (such as per form), and that supported various protocols based on lessons learned from past CRF templates. Additionally, since 2023, the Data Center has been developing a reusable reporting tool using CDISC standards for central data monitoring, while considering standardization and reporting efficiency.

These efforts led to a recognition that each group in the Data Center should work together from the earliest stages of CRF creation, to create the final deliverables, thereby facilitating organizational communication. By constructing EDC systems using CDASH-compliant CRF templates, clinical data managers can learn CDASH variables. This is becoming a standardized environment for using CDISC standards in the Data Center operations.

Implementation of CDISC Standards for Electronic Data Submission: Case Studies

The Data Center has implemented CDISC standards for three investigator-initiated clinical trials for new drug applications and one registry study, with another registry study in preparation. These registry studies serve as an external control group for clinical trials.

In study A, our first CDISC-standardized study, the Data Center outsourced SDTM creation to learn the implementation procedures. As ADaM specifications are more flexible than SDTM, our statisticians implemented ADaM. Afterwards, the Data Center participated in PMDA's trial provision of electronic clinical data submission[8] (hereafter "pilot") in 2015, and the deliverables were submitted. Although the requirement for the pilot was to provide electronic data for the items being submitted,

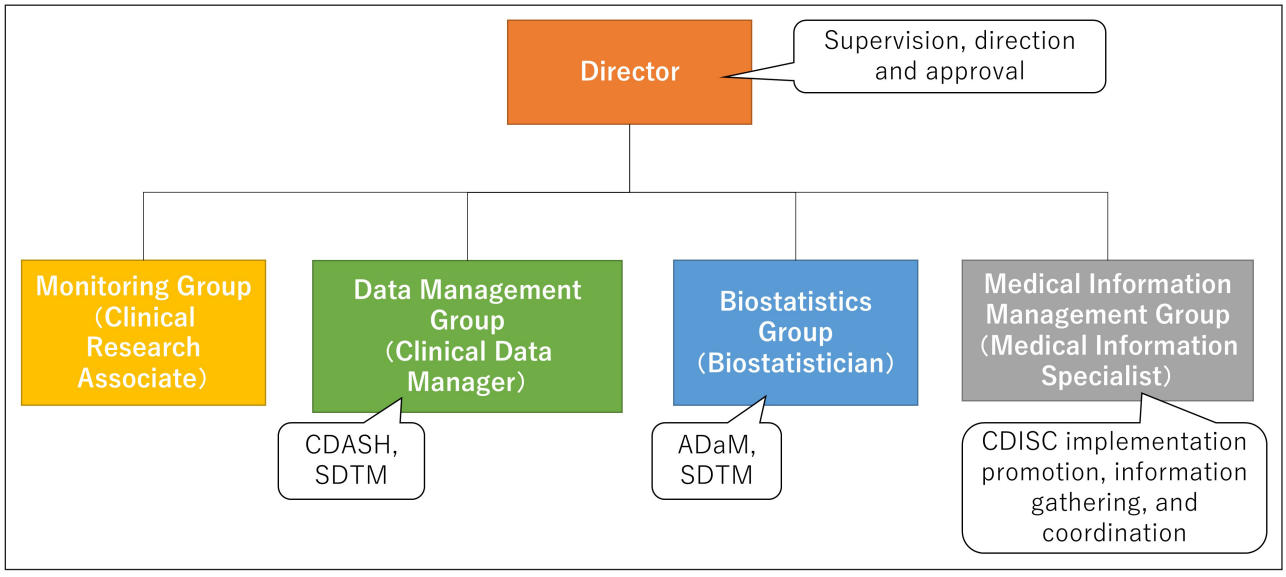

Figure 1: Tohoku University Hospital Clinical Research Data Center Structure.

the Data Center was allowed to participate as an ARO by special exception, and received feedback from PMDA that confirmed the composition of our deliverables. Based on the experiences of Study A, the Data Center learned implementation and QC procedures, and so decided to focus on in-house production for Study B (see **Table 1**).

Implementation process after Study B:

1. Agreement with Principal Investigator and applicant company
The scope of work, schedule, CDISC standards version, and need for applicant review were discussed with the Principal Investigator, the investigational drug provider, and manufacturers and distributors who apply for approval.

2. Work plan development
The Data Center prepared a CDISC work plan that described the preparation of SDTM and ADaM deliverables based on regulatory requirements from the PMDA website, the relevant Notices,[9–12] the Data Catalog,[13] and the Frequently Asked Questions (FAQ) section.[14] When preparing this plan, we referred to our experience in outsourcing Study A, the PMDA's "Explanatory Material for Electronic Data for Application (Form A),"[15] and the "Checklist for Establishing a Smooth CDISC Business Outsourcing Relationship"[16] from Data Science WG CDISC Study Team of Japan CRO Association.

3. Define data specifications
The creation of SDTM and ADaM datasets requires defining metadata, and to develop data derivation specifications requires an understanding of the SDTM and ADaM Implementation Guides (IGs),[17–18] PMDA notices, study protocols, and source data. The implementation team includes a medical information specialist as a coordinator, and the clinical data managers and statisticians in charge of the study, who are responsible for CDISC standard compliance after reading the relevant notices and completing IG training.

4. Quality control (QC)
Although data validation is performed by PMDA at electronic data submission, the data creator (strictly speaking, the applicant company) is responsible for quality based on the requirements. The metadata and SDTM/ADaM datasets will utilize Pinnacle21 Community,[19] provided that licensing permits, which is compatible with the validation tool Pinnacle21 Enterprise used by PMDA. For deliverables not covered by Pinnacle21 (Annotated CRF, SDTM and ADaM data guides), checklists were developed based on regulatory requirements.

5. Timeline management
As the workload for CDISC work took several months and ran parallel with the conventional operations of a Data Center with limited resources, managing the timeline was crucial. At the Data Center, we planned for specifications and programming to finish so that SDTM and ADaM could be created immediately after the database was locked. By starting early, and by and monitoring study progress, resource bottlenecks were avoided during critical database lock periods when conventional operations were at peak demand.

The same staff participated in Study A and Study B. Alongside the staff who had increased their proficiency level, clinical data managers who had no experience in CDISC implementation were included in Study C and Study D, acquiring skills through on-the-job training. Conversely, internal resources expected at contract time were unavailable due to staff retirements, resulting in 30% of the SDTM programming in Study C being outsourced. In light of Study B, in which frequent specification changes occurred after the SDTM specification formulation due to inexperience, the outsourcing policy for Study C was to conduct the main programming in-house to refine specifications, and then outsource SDTM programming. This, in turn, made it possible to implement outsourcing in a way that minimized rework due to specification changes.

As results of Study B, C and D—our in-house production—we calculated the time required for CDISC compliance work from the daily work hour records. In Study B, the total work time for all staff members was 16.6 months. In Study C, the total time required for the entire work was 8.8 months, and in Study D the figure was 3.7 months. This indicates a significant reduction in work time (see **Figure 2**).

In terms of the time required for meetings and coordination for study B, which was our first attempt at in-house production, scheduled monthly meetings were changed to more frequent meetings (weekly or bi-weekly)

Table 1: List of Clinical Study implementing CDISC Standards.

Type	Study A	Study B	Study C	Study D	Study E
	IIT	**IIT**	**IIT**	**Registry**	**Registry**
CDISC standard support (in-house/outsourced)	SDTM: Outsourced ADaM: in-house	SDTM: in-house ADaM: in-house	SDTM: in-house → Partially Outsourced ADaM: in-house	SDTM: in-house ADaM: in-house	SDTM: in-house ADaM: in-house
Number of in-house staffs including QC personnel	IT: 1 CDM: 2 STAT: 2	IT: 2 CDM: 1 STAT: 2	IT: 2 CDM: 2 STAT: 2	IT: 2 CDM: 3 STAT: 2	IT: 1 CDM: 3 STAT: 2
Status	Completed	Completed	Completed	Completed	In preparation

Note: IIT: Investigator-initiated (clinical) trial for New Drug Application, QC: Quality Control, IT: Medical Information Specialist, CDM: Clinical Data Manager, STAT: Biostatistician.

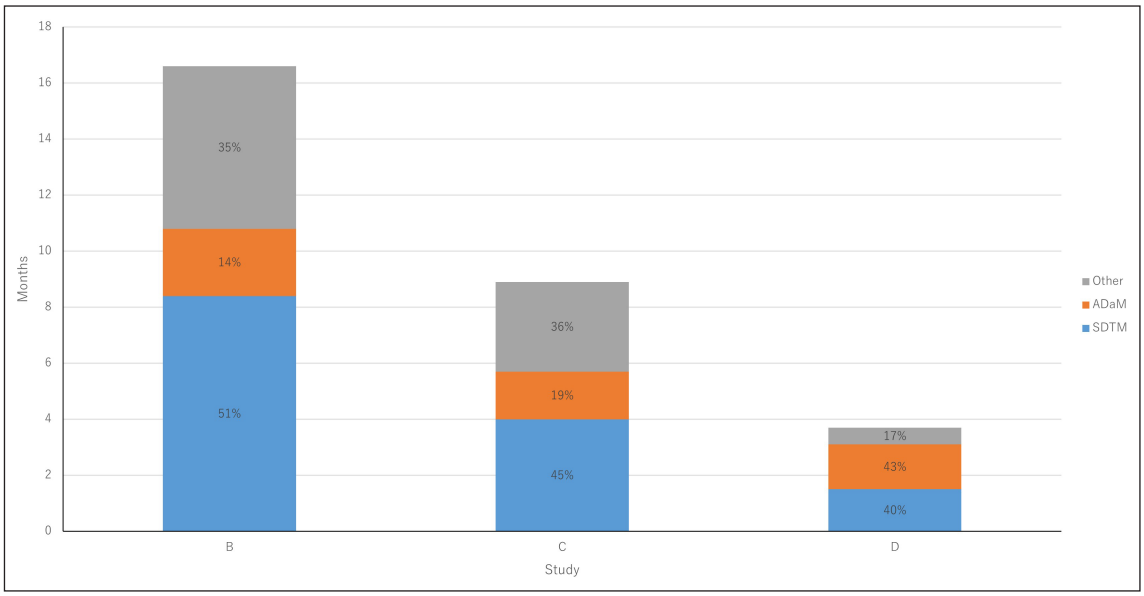

Figure 2: Time required to create CDISC standards.

Working entity	Pattern	Working process		
		Specification plan	Programming	QC
Outsourcing party	All outsourced	Outsourcing		
	Only the specification policy is made in-house Outsource everything after that	In-house	Outsourcing	
	Outsource specification development and beyond (Consulting from outsourcing party)	In-house	Outsourcing	
Own organization	Outsource specification development and beyond (Specifications are created by own organization)	In-house	Outsourcing	
	Outsource programming	In-house	Outsourcing	In-house
	Outsource part of programming	In-house	Outsourcing	In-house
	All in-house production	In-house		

Figure 3: Outline of outsourcing patterns.

for closer staff communication. The shortening of the work time for study C was due to increased proficiency, and with a CDASH-compliant CRF having simple structure from "CRF creation support". Study D, a registry study of the same diseases as Study C, had similar collection items and CRF structure, enabling the reuse of SDTM deliverables, which significantly reduced time.

Discussion

The degree of difficulty of SDTM derivation specifications varies greatly depending on the complexity of the data structure collected by the EDC system, which is the main source of data, and this is reflected in the work time. The use of standardized CRF templates in accordance with CDASH is expected to improve not only the efficiency of EDC system construction, but also the efficiency of subsequent SDTM implementation, and is a particularly effective means for organizations with limited resources to improve the quality and efficiency of the business process and achieve compliance with the requirements of the PMDA; indeed, further use of such templates is encouraged.

The decision to opt for in-house production or to outsource SDTM and ADaM in organizations with limited resources depends on the organizational strategy. Based on our experience at the Data Center, we believe that, for organizations with insufficient resources, the easiest way to introduce CDISC standards is to assign a specific person with dedicated or concurrent responsibility for consolidating knowledge of CDISC standards and accumulating experience through outsourcing. If the goal is to establish an in-house production system, one effective measure would be to gradually reduce the number of outsourced parts and increase the number of personnel who can handle them, from the upper row to the lower row of the pattern, as shown in **Figure 3**.

When outsourcing, SDTM and ADaM specifications are often subject to change due to CRF revisions by protocol amendments and the content of the data entered. Consequently, it is necessary that the contract is flexible, such as allowing for an extended period according to the period of study, and including clauses that cover the impact of potential specification changes. Prior confirmation of deliverables to be delivered is also necessary. When outsourcing work to an external contractor as the work entity, the skills and experience required to take the lead should also be confirmed as requirements at the time of outsourcing.

Conclusion

Beyond the viewpoint of "additional work" for approval application, we will continue to discuss and consider how best to utilize CDISC standards for the Data Center, and how to effectively utilize them for the AROs, based on the viewpoints of each group (monitoring, data management, biostatistics, and medical information management), and will continue to standardize, streamline, and automate operations.

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Competing Interests

The authors have no competing interests to declare.

Author Contributions

Yuko Yamada, Shih-Wei Chiu, and Takuhiro Yamaguchi led study design, study conduct, data analysis and contributed to manuscript draft. Munenori Takata, Takayo Suzuki, Saori Kanatsu, Miyuki Ishiguro, and Junya Kimura led study design, study conduct, and contributed to manuscript draft.

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