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Our challenges to save the data management cost and enhance the data quality in “Post-Marketing Surveillance”.

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ABSTRACT

In 1979, Japanese Health Authority (J-HA) has obligated pharmaceutical manufacturers to conduct a surveillance after approval to re-examine the efficacy and safety of the drug, which is called “Re-examination System”. And many “Post-marketing Surveillance (PMS)” have been conducted under the Japanese specific regulation, “Good Post-marketing Study Practice (GPSP)” through to the present day.

In the past, it was a common conception to correct more cases (such as 1000-3000) however the number of large-scale PMS has been reducing and small-scale one with specific research question increasing recently since the drug development tends to target the specific patients groups.

In the environment surrounding PMS data managers, the data collection system has shifted from paper CRF to EDC, and the data managers are required faster and more accurate data cleaning in spite of the decreasing number of cases. Accordingly, the outsourcing cost of data management is currently on the rise.

We would introduce our several achievements to save the data management cost and enhance the data quality in PMS.

INTRODUCTION

What is the “Re-examination System”?

After the drug approval, re-examination period immediately begins and continues generally for eight years. During this period, Marketing Authorization Holder (MAH) must collect the safety / efficacy data in order to report those to J-HA on a regular basis. After re-examination period ends, MAH must submit the re-examination application dossier with full results to J-HA.

What is the “PMS”?

Main purpose of PMS is to re-evaluate the drug in terms of its efficacy and safety.

Firstly, MAH submits a protocol and Case Report Form (CRF) of PMS to J-HA for approval in advance. Then, MAH starts the PMS collecting the safety / efficacy data according to the protocol under GPSP.

The data collection process is similar to clinical studies. Electronic Data Capture (EDC) system is mostly used however there are some differences due to GPSP feature.

- Obtaining Informed Consent is not required.
- Source Date Verification is not allowed.
- The support from Clinical Research Coordinator is not usual.

MAH should periodically tally all drug-related information from PMS and spontaneous reported AEs, then report them to J-HA during the re-examination period.

OUR EXERCISE OVERVIEW

Within the 14 PMSs we experienced so far, we tried the following.

1. Standardization of data Management process
   i. CRF design and database specification
   ii. Single common EDC

iii. Data management procedure

iv. Edit check specification

2. Preferred CRO system and standard outsourcing task list

3. Internal EDC development

STANDARDIZATION OF DATA MANAGEMENT PROCESS

i. CRF design and database specification

We have created the “CRF items library” that standardized CRF items with database specification. Figure 1 shows the part of CRF items library image.

Form name	Field name	Control type	Code name	Data format
Demography	Sex	RadioButton	SEX_1	1
Demography	Age	Text		3
Demography	Diagnosis	RadioButton	DIAGNOSIS_1	1
Demography	Start date of administration	DateTime		yyyy/mm-/dd-

Figure 1: CRF items library image

When designing CRF, data manager just needs to pick up the CRF items from the CRF items library. The large part of CRF and database specification can be completed simply by selecting the targeted items defined in the protocol. It makes possible less time and cost than designing CRF from scratch.

Since the PMS is a Japan-specific survey, the CRF items library is also created in Japanese, but the database specification basically conforms to CDISC and the Novartis standard database specification for clinical trial. We think that the conformation of the PMS data with the clinical trial data makes it easier to compare and analysis directly with these pre- and post-marketing data.

ii. Single common EDC

We selected the Rave EDC from Medidata Solutions as one common standard EDC for our PMS. In the past we utilized several EDCs but unified to one.
In addition, Rave EDC has a “Data entry screen replicate” function between studies within the system. Figure 2 shows the data entry screen replicate process. We used the function and process, developed the EDC system efficiently.

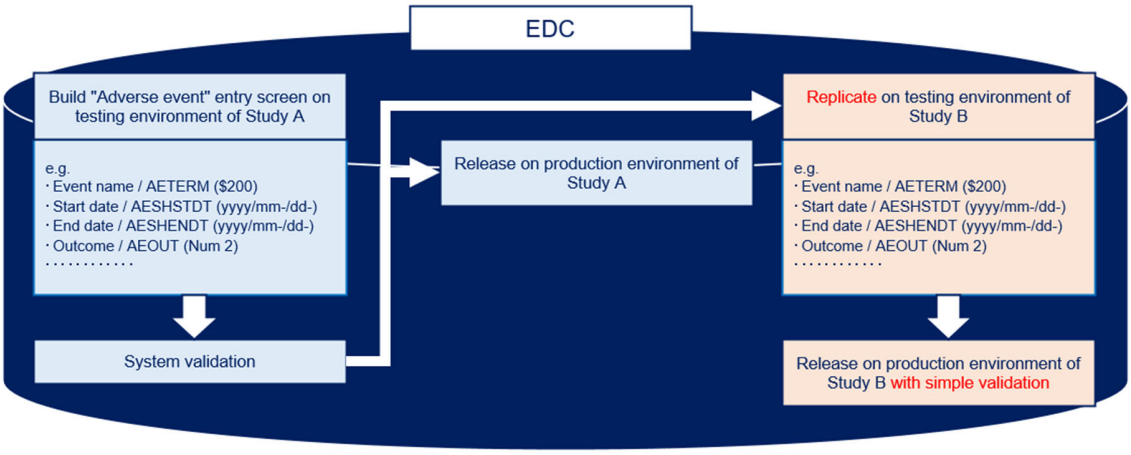

Figure 2 data entry screen replicate process

iii. Data management procedure

We have created the standard data management procedure and applied it to our Contract Research Organizations (CROs). It contributed to the process simplification and quality improvement. Figure 3 shows the structure of our standard data management procedure.

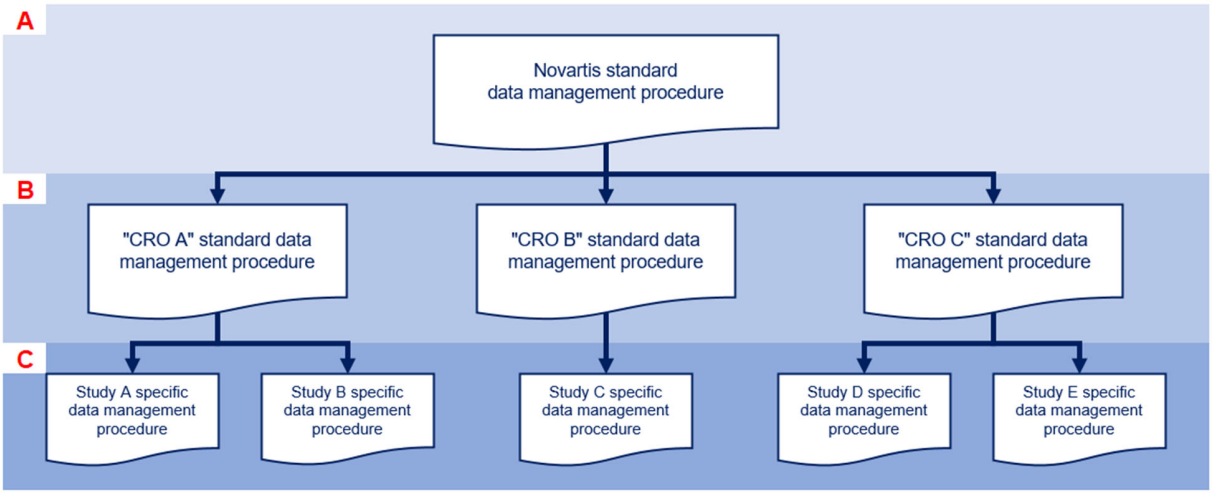

Figure 3 structure of standard data management procedure

A) Novartis data managers to create and manage standard data management procedure and provide it to each CRO.

B) Each CRO to apply the standard process to their own data management procedure.

C) Each CRO to create the study specific data management procedure to complement the standard data management procedure if required.

iv. Edit check specification

We have standardized the edit check specification. Each edit check criterion has been developed based on the CRF items library. In the past, it takes long with big efforts to create the edit check specification and programs, but the standardization has made it possible to significantly reduce those. In addition, the data quality issues due to missing of the required edit check have been significantly reduced. Figure 4 shows the relation between the "CRF items library" and "Standard edit check specification".

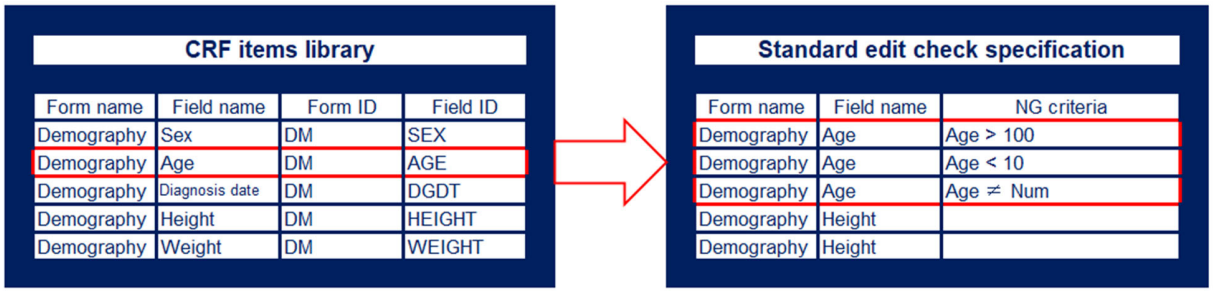

Figure 4 relations between the "CRF items library" and "Standard edit check specification"

PREFERRED CRO SYSTEM AND STANDARD OUTSOURCING TASK LIST

We have selected top three preferred CROs after performing due diligence and comparison. When the first preferred CRO cannot accept our order, the second becomes a candidate. This system can avoid our business operations risk that there is no qualified outsourcing partners when required.

Each of the preferred CROs and Novartis Japan hold the regular data management meetings to exchange information. Topic is status update, cost, quality issues etc. varies depending on the CRO, but this framework is very effective in preventing process gap among the multiple CROs. By sharing our policies and standards to all CROs through discussions, we can develop EDC and perform the data management operation successfully in a cooperative way.

In addition, we created the “Standard outsourcing task list” of PMS data management. The list defines the contents and details of data management tasks which are outsourced to CRO.

When we request for a quotation of the data management work to CRO, we roughly create a data management task list and provide to the CRO. Accordingly, the CRO lists up the detailed task for calculation, and prepares a quotation in their own format. Therefore, the quotation with task list differs as per CRO and it is often difficult to compare the prices among CROs and negotiate the reduction.

However, by using our standard task list, we can always obtain the quotations from any CRO in the same format with our standard task. The framework made it easier to compare the detailed contents and prices of each CROs quotation. In addition, it facilitated the simplification and promoted the efficiency, leading to the reduction of total price and the frequency of contract update.

INTERNAL EDC DEVELOPMENT

While many pharmaceutical companies outsource the EDC development to CRO for PMS, we have organized the in-house "Database developer (DBD) team", and two PMSs with own-built EDC are in the running phase now. The DBD team has been trained beforehand. Figure 5 shows the role-sharing between the DBD and the data manager, and the in-house EDC development period.

Development phase	Role	Implementation period (Month)
1. Planning	DBD / Data manager	0.25
2. Create specification documents	DBD / Data manager	0.25
3. Development of data entry screen	DBD	1.0
4. UAT of data entry screen	Data manager	0.5
5. Development of edit checks	DBD	2.0
6. UAT of edit checks	Data manager	1.0

Figure 5 development period

It took about five months to set up the EDC for one PMS, which is same or shorter compared to outsourcing.

ACHIEVEMENT ON OUR CHALLENGES

As a result of those our efforts, we have achieved EDC development-related outsourcing cost savings by 56% compared between before and after the introduction of standardization of data management process and preferred CROs system (Cost down 1 of figure 6). Also the outsourcing cost saved by 33% and shortened the set-up time by 20% through maintaining and improving the standard data management documents, even after introducing single common EDC (Cost down 2 of figure 6). Additionally, pursuing the standardization has minimized the operational differences among PMSs, and it has accelerated the information sharing among Novartis data managers along with the communication between Novartis and CROs, which resulted in the high PMS data quality. Furthermore, the EDC development-related outsourcing cost has been saved by almost 100% in the two PMSs that were developed in-house. Reduced the overall time spend on solving EDC development-related issues and increased in-house data manager's knowledge and skills. And the enhancement of data manager's knowledge also led to further understanding of the CRO process and appropriate communication with the CRO data managers.

PMS is a local Japanese study and typically has few opportunities to collaborate with Novartis global team. However, since we incorporated the global standard procedures into the in-house development process, there were many opportunities to collaborate with the global team. This also expedited the experience and knowledge of the in-house data managers and promote the PMS knowledge of the global team at the same time.

Those self EDC development activities finally made our data managers possible to easily solve EDC system difficulties by enhanced EDC knowledge and skills. Figure 6 shows the change of EDC development cost and period.

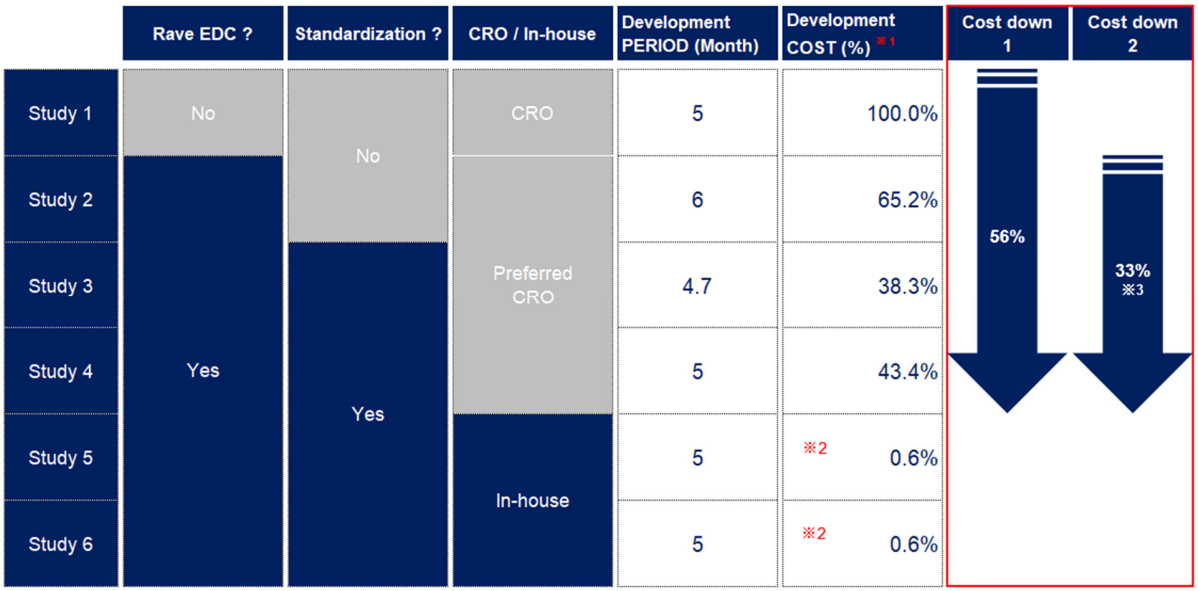

Figure 6 Change of EDC development outsourcing cost and period

※1 Including the database specification, screen design, data derivation specification, data entry manual, e-Learning development and validation.

※2 Outsourcing cost of some document creation. Not incorporating the in-house resource cost.

※3 Calculated by considering study 2 cost as baseline.

CONCLUSION

It brings many advantages to introduce the standard DM process for PMS in terms of cost and quality and further collaboration with CROs, in spite of considerable effort required when applying and maintaining the standard documents on a regular basis in the fast-changing environment. Now we can meet the diversified needs of PMS design with in-house EDC. We anticipate further changes of external environment and adoption of emerging technologies such as artificial intelligence for data management operation, our effort of driving the process improvement and new challenge continues in future.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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