

## Case Report Form (CRF) Design Made Easy: An Evaluation of Clinical Data Acquisition Standards Harmonization (CDASH) in Use

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**Abbreviations:** CDISC: Clinical Data Interchange Standards Consortium; CDASH: Clinical Data Acquisition Standards Harmonization; CRF: Case Report Form; CDM: Clinical Data Manager; PI: Principal Investigator; SDTM: Study Data Tabulation Model; UICC: Union For International Cancer Control; JSCCR: Japanese Society For Cancer Of The Colon And Rectum

### Introduction

The standardized formats of clinical research data have been developed and established by the Clinical Data Interchange Standards Consortium (CDISC), which is addressing standardization in order to support the acquisition, exchange, submission, and archive of clinical data from individual trials and their metadata [1]. CDISC has developed the Clinical Data Acquisition Standards Harmonization (CDASH), which is a standard for data collection [2-4]. Data reliability, integrity, and exchangeability for clinical research depend greatly on having accurate and uniform definitions of the data items to be collected and the design of case report forms (CRF). The use of CDASH is very helpful for standardizing the items and data formats in a CRF for any trial across different research institutions.

Although CDASH is considered as a breakthrough to control the quality of CRFs, its implementation has scarcely been reported for actual clinical trials and its practicality has not been sufficiently discussed. Therefore, we present a report of using CDASH to design a CRF, an evaluation of its usefulness, and a discussion of our experience and findings.

### Methodology

In this study, a medical student, with no experience of clinical trials, was given the task of designing a CRF using CDASH in order to evaluate its usefulness. The process of the study, which was implemented by only one student, is composed of 3 stages; training, production, and evaluation.

First, in the training stage, the student went through a training process to learn about clinical trials, CRF and CDASH. An experienced clinical data manager (CDM) lectured the student about clinical trials, how CRF and CDASH work in clinical trials, and how to use each standard. The training course was held for 2-3 hours, every 2 weeks, for 2 months. After finishing the course, the student read 3 manuals for self-study: CDASH Standard [2], CDASH User Guide [3] and Library of Example CRFs [4].

Next, in the production stage, the student was given the protocol and independently designed the CRF. The applied protocol was of a colorectal cancer clinical trial conducted in the University of Tsukuba Hospital and the Tsukuba Medical Center Hospital. This study was an open-label, single arm, therapeutic exploratory, phase I study. In total, 100 patients with colorectal cancer will be recruited from the University of Tsukuba Hospital and the Tsukuba Medical Center Hospital, and enrolled into the study if they meet the eligibility criteria. Ethical approvals were obtained from the Research ethics committees at the two centers. Patients enrolled in this study will receive daily

clinical practice, be collected clinical data (demographics, medical history, laboratory examinations, previous/concomitant medications and imaging test). This study aims to evaluate the immunosuppressive function in colorectal cancer patients. No particular criteria were used when choosing the protocol, because CDASH describes the basic data collection fields for 18 general domains such as 'Demographics' and 'Adverse Events', which are common to almost all protocols. A Principal Investigator (PI) in the trial and the CDM decided the data items of CRF. After the student received the data items from the CDM, the student searched CDASH for the appropriate parts to explain each data item and mapped the variables to the CRF. The data items defined in the protocol are listed in Table 1. When the items were not defined in CDASH, Study Data Tabulation Model (SDTM) standards were used instead [5]. For more detailed process of CRF design, see Appendix 1.

Finally, in the evaluation stage, the CDM evaluated the CRF designed by the student. The variables mapped in the CRF were compared with those defined in CDASH. To evaluate the performance of the designed CRF, we analyzed its concordance with CDASH. When the CDISC-defined part of the variable was identical, the item was counted as concordant. For detailed concept of this definition, see Appendix 2.

### Results

The data items defined in the protocol, the domain of the data items, and the named variables by the student are listed in Table 1. A total of 52 data items were defined in the protocol. All the items were correctly categorized into 9 domains (Common Identifier Variables, Disposition, Demographics, Inclusion/Exclusion Criteria Not Met, Laboratory Test Results, Prior/Concomitant Medications, Substance Use, Tumor Identification and Tumor Results) and were accurately reflected in the CRF. Of the items, 30 were found in the CDASH manual and the remaining 22 were not; for these items categorized in domains 'Tumor Identification' and 'Tumor Results', we referred to SDTM. All the 52 items were named by the student according to CDASH or SDTM. However, of 52 items, 6 items categorized in the 'Inclusion/Exclusion Criteria Not Met' domain were incorrectly named. Excluding this domain, the concordance proportions of the other 8 domains were 100% (Table 1). The concordance proportions by each domain were as follows: Common Identifier Variables: 100%

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Contents of CRF	Domain of CDASH	Variable name of CDASH	Variable name (student)	Concordance proportion
What is the site identifier?	Common Identifier Variables	SITEID	SITEID	100 % (3/3)
What is the subject identifier?		SUBJID	SUBJID	
What is the investigator identifier?		INVID	INVID	
What was the date of informed consent?	Disposition	DSSTDAT	DSSTDAT_informedconsent	100 % (2/2)
What was the date of registration?		DSSTDAT	DSSTDAT_registration	
What is the subject's age?	Demographics	AGE	AGE	100 % (2/2)
What is the sex of the subject?		SEX	SEX	
Inclusion Criteria 1	Inclusion/Exclusion Criteria Not Met	IEORRES	INC_001	0 % (0/6)
Inclusion Criteria 2		IEORRES	INC_002	
Inclusion Criteria 3		IEORRES	INC_003	
Inclusion Criteria 4		IEORRES	INC_004	
Inclusion Criteria 5		IEORRES	INC_005	
Exclusion Criteria 1		IEORRES	EXC_001	
What was the lab specimen collection schedule date?	Laboratory Test Results	LBDAT	LBDAT_specimen	100 % (4/4)
What was the lab specimen collection date?		LBDAT	LBDAT_tumor_marker	
What was the result of the test?		LBORRES	LBORRES_tumor_marker	
What were the units for the result?		LBORRESU	LBORRESU_tumor_marker	
Did the subject take chemotherapy?	Prior/Concomitant Medications	CMOCCUR	CMOCCUR_chemotherapy	100 % (6/6)
What was the term for the listed oral chemotherapy taken?		CMTRT	CMTRT_chemotherapy_ORAL	
What was the term for any other oral chemotherapy taken?		CMTRT	CMTRT_chemotherapy_ORAL_others	
What was the term for the listed intravenous chemotherapy taken?		CMTRT	CMTRT_chemotherapy_INTRAVENOUS	
What was the term for any other listed intravenous chemotherapy taken?		CMTRT	CMTRT_chemotherapy_INTRAVENOUS_others	
Did the subject take steroids?	CMOCCUR	CMOCCUR_steroid		
Has the subject ever used tobacco?	Substance Use	SUNCF	SUNCF_TOBACCO	100 % (7/7)
What was the duration of tobacco use?		SUCDUR	SUCDUR_TOBACCO	
What was the frequency of tobacco use?		SUDOSFRQ	SUDOSFRQ_TOBACCO	
Has the subject ever used alcohol?		SUNCF	SUNCF_ALCOHOL	
What was the duration of alcohol use?		SUCDUR	SUCDUR_ALCOHOL	
What was the amount of alcohol used?		SUDSTXT	SUDSTXT_ALCOHOL	
What was the frequency of alcohol use?		SUDOSFRQ	SUDOSFRQ_ALCOHOL	

Where was the location of the tumor?	Tumor Identification *	TULOC	TULOC	100 % (1/1)
What was the longest diameter of the tumor?	Tumor Results * ***	TRORES	TRORES_longest_diameter_along_major_axis	100 % (21/21)
What was the width of the tumor? (Perpendicular to the longest diameter)		TRORES	TRORES_longest_diameter_perpendicular_to_previous_one	
What was the clinical assessment of T** of the tumor according to the Japanese Classification of Colorectal Carcinoma? (JSCCR)		TRORES	TRORES_clinical_T	
What was the clinical assessment of N** of the tumor according to JSCCR?		TRORES	TRORES_clinical_N	
What was the clinical assessment of M** of the tumor according to JSCCR?		TRORES	TRORES_clinical_M	
What was the stage of the tumor? (Clinically assessed according to JSCCR)		TRORES	TRORES_clinical_stage	
What was the pathological assessment of T of the tumor according to JSCCR?		TRORES	TRORES_pathological_T	
What was the pathological assessment of N of the tumor according to JSCCR?		TRORES	TRORES_pathological_N	
What was the pathological assessment of M of the tumor according to JSCCR?		TRORES	TRORES_pathological_M	
What was the stage of the tumor? (Pathologically assessed according to JSCCR?)		TRORES	TRORES_pathological_stage	
What was the histopathological type of the tumor according to JSCCR?		TRORES	TRORES_pathological_histological_stage	
What was the clinical assessment of T** of the tumor according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours?		TRORES	TRORES_UICC_clinical_T	
What was the clinical assessment of N** of the tumor according to UICC?		TRORES	TRORES_UICC_clinical_N	
What was the clinical assessment of M** of the tumor according to UICC?		TRORES	TRORES_UICC_clinical_M	
What was the stage of the tumor? (Clinically assessed according to UICC)		TRORES	TRORES_UICC_clinical_stage	
What was the pathological assessment of T of the tumor according to UICC?		TRORES	TRORES_UICC_pathological_T	
What was the pathological assessment of N of the tumor according to UICC?		TRORES	TRORES_UICC_pathological_N	
What was the pathological assessment of M of the tumor according to UICC?		TRORES	TRORES_UICC_pathological_M	
What was the stage of the tumor? (pathologically assessed according to UICC)		TRORES	TRORES_UICC_pathological_stage	
What was the histopathological grade of the tumor according to UICC?		TRORES	TRORES_UICC_pathological_differentiation	
What was the macroscopic classification?		TRORES	TRORES_gross_stage	

\* 'Tumor Identification' and 'Tumor Results' domains are defined in SDTM [5].

\*\* T, N, and M are defined as 'The extent of the primary tumour,' 'The absence or presence and extent of regional lymph node metastasis' and 'The absence or presence of distant metastasis' according to International Union Against Cancer (UICC) TNM Classification of Malignant Tumours [6].

\*\*\* The contents of CRF in the 'Tumor Results' domain are defined according to International Union Against Cancer (UICC) TNM Classification of Malignant Tumours or Japanese Classification of Colorectal Carcinoma by Japanese Society for Cancer of the Colon and Rectum (JSCCR) [6,7].

**Table 1:** The data items defined in the protocol.

(3/3); Disposition: 100% (2/2); Demographics: 100% (2/2); Inclusion/Exclusion Criteria Not Met: 0% (0/6); Laboratory Test Results: 100% (4/4); Prior/Concomitant Medications: 100% (6/6); Substance Use: 100% (7/7); Tumor Identification: 100% (1/1); and Tumor Results: 100% (21/21).

## Discussion

Surprisingly, the concordance proportion was very high, except for the 'Inclusion/Exclusion Criteria Not Met' domain. With regard to this domain, the mismatch may have occurred due to the student's misunderstanding of Inclusion/Exclusion Criteria in CDASH and the variable name that the student used for this domain was found in the Library of Example CRFs published by CDISC. 'Inclusion/

Exclusion Criteria Not Met' domain is different from other domains due to insufficient explanation about mapping the variables. Because CDASH does not define specific variables regarding this domain, it is difficult for beginners to correctly map them. On the other hand, the explanations to map unambiguous variables of the other 8 domains are very easy to understand, even for beginners. The description of the variables in 'Inclusion/Exclusion Criteria Not Met' domain should be modified to be user-friendly.

The incompleteness of the CDASH standards themselves could decrease the concordance. In our case, some data items in the protocol corresponded to the Union for International Cancer Control (UICC) guidelines and Japanese Classification of Colorectal Carcinoma (JSCCR) [6,7]. These data items were categorized in 'Tumor Results'

domain. However, detailed data items such as What was the stage of the tumor? (Clinically assessed according to UICC) were not provided in CDASH and SDTM standards. In other words, disease specific variables are not provided in these standards. Therapeutic Area Standards are currently being developed to provide variables and items in each disease area [8]. While some standards are already available, the standardization for colorectal cancer has not yet been completed.

### Limitations

There are two limitations in this study. First, the limitation of this study is it did not meet Tier 2 of the 2 levels of conformance to CDASH. Tier 1 evaluates the conformance at the CRF level and Tier 2 evaluates at the operational level [2,3]. We met only the Tier 1 level of conformance, because we did not apply the designed CRF to actual data collection. Second, because this is a case report, it is necessary to increase the number of subjects in experiment to obtain generalizable result.

### Conclusion

Through our study we have confirmed that CDASH standard is useful to design CRFs, especially to design general domains such as 'Demographics' and 'Adverse Event'. It is also easy for researchers who do not have much experience in clinical trials to use the CDASH standard.

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### Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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