

## **PharmaSUG2010 - Paper HS01**

### **CDASH Standards for Medical Device Trials: CRF Analysis**

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The pharmaceutical industry is rapidly adopting the Clinical Data Acquisition Standards Harmonization or CDASH for standardization of data acquisition processes. Unlike the pharmaceutical industry, the medical device industry does not have standardization of data collection and submission. Considering benefits like efficient study reporting, faster data processing and faster regulatory reviews, the Clinical Data Interchange Standards Consortium (CDISC) is in the process of evaluating applicability of CDASH to medical device trial data and in analyzing the need for amendments in these standards so that they can meet the needs of the medical device industry. There are similarities as well as substantial differences in terms of purpose and perspective of the data collected in drug trials and those collected in medical device trial. To assess these differences from data collection perspectives, CDISC assigned preliminary research related to data collection in medical device trials to a team of individuals from both CDISC and medical device companies.

This paper provides brief overview of the CRF analysis project and elaborates on key findings revealed by the analysis. It also summarizes the findings of CRF frequency analysis with respect to standard clinical domains defined by CDASH. Results of this analysis reveal direct application of most of the CDASH domains developed for drug trials to medical device trials

### **Introduction**

Pharmaceutical industry has rapidly adopted the submission data standards and there are growing efforts to standardize the data management in upstream activities by providing robust

standards like CDASH. While things look really streamlined and promising in pharmaceutical industry, there is very little or no standardization in terms of submission or data acquisition in the medical device industry. Although many sponsors often have some degree of standardization for internal processes, such standardization may provide efficiencies in terms of internal processes only. For faster and efficient regulatory reviews, it is important to have standardization across industry.

The CDASH leadership and the group responsible for maintenance of CDASH decided to assess the applicability of these standards on medical device trials. This was an important preliminary step to evaluate the need for separate version of CDASH for medical device trials. Most of the participants in this initiative are individual volunteers from different sponsor and vendor companies working on medical device trials. Leadership of this team decided to form a sub-team more focused on CRF frequency analysis to evaluate applicability of existing CDASH standards on the medical device trial data collection process. By eliminating identity specific information, some sponsor and vendors contributed to these efforts by providing sample case report forms for this frequency analysis. Individual volunteers working on CRF analysis used these forms and compared the data collection mechanism against the provisions in the existing CDASH standards. This assessment method and overall work of the CDASH team is described below.

### **Methodology and Conduct for CRF Analysis**

As an initial step, the CRF analysis team divided the CRFs based on the type of information collected on each page. This was an effort to align the CRF data collection pages with the standard domains defined in CDASH to facilitate one on one comparison of domains against CRF pages. In this process, one hundred and seventy CRF pages were analyzed and assessed for their relevance with existing CDASH domains Meta data. Out of these, 138 CRF pages could be directly aligned to existing CDASH domains. These were further categorized into standard safety domains defined by CDASH. Resulting categorization of CRF pages as per CDASH domains is provided in the table below. As it can be observed from this table, the CRFs analyzed were part of different trials. Above categorization of CRFs provided sufficient input to start off with further analysis steps.

As a first step a reporting and tracking mechanism was developed by using Microsoft Excel spreadsheet. Such mechanism was envisioned to provide necessary input for documentations of all findings in details. Some of the key fields included in this mechanism are:

- Domain name: Aligned with the domain names proposed in existing CDASH models for drug trials.
- Device/Data collection field and label: This is the detailed description of field as stated in the CRF.
- Is the question in CDASH (yes/no/possible):
- Is the question 'same' in CDASH (yes/no/possible):
- Are answers same in CDASH

Guideline used for verifying answer status in CDASH questions was to mark, i) 'yes' if there is a direct relevance of description with the verbiage in existing CDASH guidelines, ii) 'no' if no information exist in CDASH, and iii) 'possible' if there is a resemblance of information provided in CRF with the variable information described in CDASH. Analysis,

categorization, and conclusion based on discussions regarding above variables was a core essence of frequency analysis.

### Number of CRFs Analyzed by Domain

Domain	Number of CRF Pages
AE	25
CM	9
DM and SC	9
DS	16
EG	1
Imaging	10
IE	13
LB	9
MH	10
PE	1
DV	4
QS	20
SU	2
VS	2
Operative CRFs	3
Other	4
	Non-pharmacologic treatments-2, Comments-1, Diagnosis-1

- Comments: This field is aimed to collect details about the possible response collection on CRF, and number of CRFs in which such variable or field was observed.
- CDASH standard variable name: This field is aimed to populate only if the data collection field on CRF page directly resembles the CDASH variable name.
- Core designation in CDASH (highly recommended/ Recommended-conditional/optional): This information needed to be documented thoroughly to get the necessary input required to map the data collection fields against existing drug oriented CDASH.
- Frequency of appearance in Device forms (# times seen / # forms examined, can equal more than one page):
- Recommend inclusion in CDASH? (yes/no/na -if already there).  
Reason for inclusion or exclusion: Recommendation about inclusion of such field as a 'variable' in CDASH: Such recommendation needed strong rationale behind such proposed inclusion of data collection fields to CDASH. In some cases, where CRF subgroup couldn't confirm the treatment of variable, such cases were brought to the attention of the larger group working on CDASH standards for medical device.

Tracking mechanism with above fields with necessary rationale was finalized in the initial kick off meeting of the group. During this meeting, the group distributed the domains among the team members. Depending on complexity of domains, each member agreed to map and analyze roughly three to four domains. Series of weekly or in some cases bi-weekly teleconferences were organized to analyze and discuss the findings and propose final summary. With the above approach, it was easy for the members of this team to analyze and thoroughly evaluate each CRF page, map the information from the CRF page to appropriate variable, and compare the meta-data against existing CDASH standards. To get added perspective in reporting, submission data standards (SDS) were also referred.

### Findings: Similarities and Differences

As described above, the CRF sub-team started their work with a set of nicely organized 138 CRF pages contributed by different sponsor companies, mutually agreed upon tracking mechanism and method for conduct for analyzing the CRF pages, and pre-defined frequency of teleconferences. This work was completed during May 21<sup>st</sup>, 2009 till 9<sup>th</sup> October, 2009 and the sub-group needed to plan 16 tele-conferences, each one lasting for approximately an hour or so. As a first step, overview of this analysis was developed. Such overview is provided below:

### Comparison of CRF Fields against CDASH

CDASH Domain	Total number of CRF Fields	Number of CRF Fields which		
		Could be mapped to CDASH variables	Correspond to 'highly recommended' variables in CDASH	Were considered for further discussion
IE	42	18	12	12
DM	54	23	7	8
DS	29	13	5	16
CM	53	47	15	6
AE	349	176	109	30
MH	70	28	7	4
LB	76	28	22	0
VS	10	8	6	2
DV	21	11	3	10
PE	3	3	3	0
SU	10	10	2	0
EG	4	4	4	0

Domain specific findings and a quick overview of observations is stated below:

Inclusion/Exclusion criteria: Most of the information from CRF pages could be mapped to CDASH highly recommended variables such as 'IEYN', and 'IETESTCD'. In some cases, CRF listed detailed criteria corresponding to variable 'IETEST'. There were 3 unique fields which appeared in 4 different CRF pages, which were not captured in CDASH. This was taken for

further discussion. Later these fields were not considered in CDASH mainly because they were aimed to collect compliance data rather than clinical data.

Demog: There was lot of variations found with the way this data is being collected by medical device industry. Some CRF fields were design to collect the data, which is usually collected in different domains like Vital signs, medical history, and lab as per CDASH standards. There were 8 different fields finalized for further discussion. Later CRF sub-team concluded that such fields were not collecting core clinical data and it is not advisable to include such fields in CDASH.

Discontinuation: Variations in data collection practices were observed in terms of different practices of treating discontinuation data. There were 14 different CRF fields which were considered for further discussion. There were couple of fields related to 'patient counts', which could have been very specific to sponsor requirements. CRF sub team concluded that such information can be derived from Exposure data and it is not necessary to have a separate field defined in CDASH for that purpose. Some of the data collection fields were found to collect administrative data and in some cases it is observed that the data collection fields are collecting redundant data. Such fields were not considered for inclusion in CDASH.

Concomitant medication: This domain was most finely aligned with existing CDASH standards. Out of 53 fields found in different Con-med CRF pages, corresponding variables of 47 fields exist in CDASH. There were 6 fields considered for further discussion but were excluded from consideration in CDASH as these fields seemed to collect redundant data.

Adverse Event: This was one of the most complex and challenging domain for frequency analysis. There were 349 data collection fields to be analyzed. 'Device operator' added a dimension to the established concept of adverse event relations and emergence as defined in drug trials. Things like 'device malfunction', 're-operations', and 'un-anticipated product failure' gave lot of new considerations in the data collection fields and mechanism defined in CDASH. Despite these substantial differences, it was observed that 176 fields from these CRF pages were already aligned to data collection variables defined by CDASH. Out of these, 109 fields were 'highly recommended' as per the CDASH guidelines. There were close to 30 fields, which CRF sub team decided to discuss with larger group. Asides that there were about 12 fields which occurred with very low frequency and were specific to operator specific data collection. CRF sub-team decided to exclude such low frequency fields because of lack of sufficient consensus required to justify inclusion of such field in CDASH. Results of further discussion on these fields are explained in the subsequent section.

Medical History: Out of 70 distinct field analyzed in medical history CRF pages, there were lot of variations observed in the data collection mechanism. Many fields were design to collect sponsor specific data. Although CRF analysis sub team concluded not to change the CDASH model because of lack of consensus on findings, it was concluded that certain fields such 'completion date' or 'if medical history findings are on-going' need more discussion.

Lab: There were 76 distinct data collection field observed across 10 CRF pages. Out of these 28 could be directly aligned to CDASH and 22 fields reflected as 'highly recommended' variables as per CDASH. Most of the other fields which were not defined as per CDASH were chose not

to be included in CDASH mainly because most of them were designed to capture either sponsor specific data, or were design to capture the data which CDASH captures as a part of different domains, or because some of them did not provide enough consensus to justify their inclusion in CDASH.

**Vital Signs:** These data collection fields were aligned to CDASH model. There were only two fields in vital signs which were not defined by CDASH. One of them was a ‘ventilation mode’, which is used very uncommonly and doesn’t justify inclusion in CDASH. Second field was about condition on vitals measurement, which seemed to be derived information rather than data collection information. Because of above reasons, these two fields were not considered for inclusion in CDASH.

**Protocol Deviation:** In this domain, out of 21 distinct fields, 11 fields were directly aligned to the CDASH model. Out of these 11 fields, 3 fields were ‘highly recommended’ as per CDASH terminology. Out of remaining 10 fields, most of the fields were not chose to include in CDASH because of either those were sponsor specific fields or because those fields were collecting identification details such as ‘date’. One of the field collecting ‘deviation type’ was decided to be brought to the attention of larger group to decide importance of separation of deviations from ‘errors’, and to decide categorization of human vs machine errors.

**Physical Examination, Substance Use, and ECG:** There were only 3 fields observed in ‘Physical Examination’ domain and all these fields were already defined in CDASH under ‘highly recommended’ categorization. Similar to this, Substance use (10 fields) and ECG (4 fields) were align to the CDASH model.

As discussed above, most of the standard safety domain specific fields related information could be easily related or mapped to existing CDASH standards or did not provide enough consensus to modify existing CDASH standards. Based on available data and its clinical significance CRF sub team found that it is important to discuss certain fields in the larger group for appropriate decision. Some of these key findings are discussed in the following session.

## **Key Findings**

Certain fields on the CRF forms needed more discussion to decide their impact of existing CDASH standards. Such cases are very unique and are specific to certain safety domain.

- **Deviation check type:** This field related to protocol deviation page was aimed to collect causes of deviation. In the sample CRF forms analyzed, there was consistency about the possible options or data collection fields in different forms. Primary cause of deviation was broadly categorized as either ‘human errors’ or ‘instrument’ error. Further sub-categorization of information collection based on the instrument properties and timing of use. Initial thoughts of CRF team were to separate deviations from errors and segregate machine related errors and human errors. CRF sub team proposed a thought of including such machine errors as a part of device malfunction domain. This finding is still under discussion.

- Medical history field- Status: Couple of CRF collected the status of medical history in terms of if the medical history related conditions are still ongoing. Currently this information is being collected in terms of CDASH variable of 'MHONGO'. CRF sub team reached to a conclusion that based on the current consensus it is not advisable to modify the CDASH standards and rather leave the collection field options to be modeled by the sponsor. This was a good decision as 'MHONGO' is an optional field as per CDASH guidelines.
- Medical history completion date: CDASH has an optional data collection field as 'MHSTDAT' which is designed to collect such information. The discussion about this collection field was initiated because of surgical history and possible specialization of medical history collection forms depending on different therapeutic areas. This was chosen to be discussed in larger group to see if there are categories of fields that might be useful for defining some structure around the surgeries, as currently these don't fit the structure of CDASH.
- Adverse Events- Did product failure or malfunction contribute to the event? This collection field appeared in multiple forms. Inclusion of this in CDASH would pertain addition of variable. Need of such addition is under discussion with the CDASH team.

## **Conclusion**

Standardization of data collection for medical device trials is important for efficient data collection process. Based on CRF analysis conducted by CDASH team, existing CDASH standards can be easily applied on medical device trials. As discussed above many CRF fields could not be considered for further discussion because of lack of consensus. It is important that the medical device industry actively contributes to this process to ensure that the standards developed by CDASH reveal broader applicability and relative ease in implementation. CDASH committee is giving due considerations to the data collection fields which do not exist currently in CDASH. In order to maximize the benefits that can be achieved through standardization, CDASH group working on these standards is looking forward for enough data to support the decisions.

## **Reference**

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