Clinical Data Acquisition Standards Harmonization

Package-3

Drug Accountability & Exposure (DA & EX)

Comments & Protocol Deviations (CO & DV)

Disposition (DS) or End of Study

Collaborative Group Review

December 2007

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Section 1. Collaborative Group Review Process and Instructions

1. CDASH Package-3

CDASH Package-3 contains basic data collection variables for the Drug Accountability & Exposure (DA & EX), Comments & Protocol Deviations (CO & DV) and Disposition (DS) or End of Study. Each Harmonized Version (HV) contains the following sections:

- Introduction and Background
- Table 1: Highly Recommended Data Collection Variables
- Table 2: Recommended / Conditional
- Table 3: Optional Data Collection Variables
- Table 4: Examples of Data Collection Variables Generally Considered Not Necessary to Collect

1.1 Review Process

The review of the following basic data collection variable tables should answer at a minimum the following questions:

Do the proposed data variables cover the basic variables common to most clinical research?

Is the document, taking into account the above, appropriate for broader public review?

1.2 Comment Process

A package consisting of 3 HVs and an Excel comments spreadsheet will be sent to each Collaborative Group (CG) member for distribution within their respective organizations.

We request that each organization consolidate all comments from into one Excel spreadsheet. Be sure to provide the identifying information for each comment (see example below).

Example:

Num	*Reviewer*	*Affiliation*	*Domain*	*Page*	*Variable Name*	*Suggested Change*	*Rationale*
1	*John Smith*	*ABC Pharma*	*DA*	*5*	*DATEST*	*Typo*	*editorial*

Please send consolidated comments to scamhi@cdisc.org no later than 07 January 2008.

Comments will be addressed and a "Reviewed Version" will be then achieved.

2. Introduction

This document contains the third of four Clinical Data Acquisition Standards Harmonization (CDASH) Packages to be submitted for Collaborative Group (CG) review. CDASH Package-3 consists of Harmonized Versions (HV) for the following domains: Drug Accountability & Exposure (DA & EX), Comments & Protocol Deviations (CO & DV) and Disposition (DS) or End of Study.

The Clinical Data Interchange Standards Consortium (CDISC) Operating Procedure (CDISC-COP-001 Standards Development) is the basis for the CDASH process. The Initial Consensus Versions or Harmonized Versions (HVs) were developed by the respective work streams. The HVs included with this document have been reviewed internally by the CDISC Technical Leadership Committee (TLC), comments have been addressed to produce these HVs. The next step in the CDISC consensus-based standards development process is the external focused review or in this case the Collaborative Group review.

The comments from this Collaborative Group review will be collated and each will be addressed. Once all of the HVs from each of the 14 domains have been reviewed by the Collaborative Group and all comments have been addressed, the resulting 14 domains will be posted on the CDISC website for public review. After comments have been addressed CDASH Version 1.0 will be released.

3. Best Practice (General Recommendations and Observations Applicable to all Domains)

3.1 Implementation of CDASH Recommendations

The CDASH project seeks to identify the basic data collection fields needed from a clinical, scientific and regulatory data collection perspective, to enable efficient data collection at the investigative sites. Clearly, the more data fields that are collected, the greater the chances of introducing and/or not identifying errors and the greater the resources needed for monitoring, auditing, conduct and management of the project. Hence, while the Study Data Tabulated Model (SDTM) provides a standard for a 'superset' of data that could potentially be collected or derived, CDASH intentionally identifies a basic set of highly recommended and recommended variables or data collection fields that are expected to be present on the majority of case report forms (CRFs). Although it is assumed that additional data fields will be needed to address the study requirements, this approach forces a thought process among sponsors to determine specifically which fields, if any, must be added to these CDASH recommendations based upon the protocol and the business practices of the sponsor. Specifically, until therapeutic area-specific (TA) data fields have been standardized, these variables will need to be added to the CDASH recommended fields to fulfill the protocol-specific requirements.

While SDTM and CDASH are clearly related, there are instances where they do not exactly match due to their varied purposes, (submission vs. data collection). For example, the SDTM standard may contain derived data while CDASH variables should not be derived at the data acquisition stage. Basic data collection fields identified by CDASH project teams (via the CDISC consensus process) are mapped into the SDTM and are compliant with the SDTM IG. As part of this mapping the SDTM core designation (e.g., required, expected, permissible) has also been provided where applicable as an aide to reviewers. All SDTM "required" data collection fields have been addressed in the CDASH recommendations. The CDASH work streams have intentionally not reproduced other sections of the SDTM standard, and reviewers are asked to refer to the CDISC SDTM Implementation.

CDASH can be viewed as a compliment to the SDTM. The goal to identify a list of basic data collection fields which Sponsors may use as needed to meet protocol specific and other data collection requirements, (e.g. therapeutic specific (TA) data fields and others as required per protocol, business practice and operating procedures).

3.2 Terminology

Terminology used by the CDASH project is developed through the CDISC Terminology Team and is published by the National Cancer Institute's Enterprise Vocabulary Services (NCI EVS). The CDASH final document, will only list the name of the code list stored in NCI's EVS. *(http://cdebrowser.nci.nih.gov/CDEBrowser/)*

Terminology proposed by the CDASH project will be forwarded to the CDISC Terminology team for consideration and vetting via the consensus-based development process.

PROTOCOL DEVIATIONS & COMMENTS STREAM

Harmonized Version

Stream Leader: Jay Leeka, AstraZeneca

Co-Stream Leader: Rinske Sieders, Astellas Europe

19 November 2007

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Section 2. Protocol Deviations & Comments Stream ICV Version

1. Introduction

The CDASH Protocol Deviations & Comments stream was comprised of 28 members from the following organizations: Amgen, Astellas Europe, AstraZeneca, Boston Scientific, CSS Informatics, Eisai Global Clinical Development, CV Therapeutics, Eli Lilly and Company, Ethicon (Johnson & Johnson), Fast Track Systems, Forest Laboratories, Merck & Company, Metacure (USA), National Cancer Institute Center for Bioinformatics, NIH Office of Biotechnology Activities (OBA), Novartis, OmnicareCR, Parexel International, Phoenix Data Systems, Schering-Plough, and Schwarz BioSciences; representing the following job functions: Data Management, Data Standards Development and Governance, Biostatistics, Programming, Clinical Informatics Training, Clinical Operations, Quality Assurance, Clinical Project Management and Clinical Consulting.

The Protocol Deviations and Comments Stream began by reviewing industry Case Report Form (CRF) samples submitted by stream members, which captured either Protocol Deviations or Comments information. The stream members also collected feedback from numerous functional areas within their respective companies to identify their purpose in collecting protocol deviations and comments data. The stream listed the fields or variables captured on the collected CRFs, also noting any associated value lists as well as the method of data collection (paper or Electronic Data Capture (EDC)). The SDTM variables served as a target for deliverable data and all data variables were mapped to the SDTM variables where applicable. Regulatory requirements were reviewed and discussed and included in the proposed process for dealing with both Protocol Deviations and Comments data collection.

2. Comments CRF

The team arrived at the decision to classify comments as either solicited or unsolicited.

2.1 Solicited Comments

Solicited comments are defined as those entered in free-text fields intentionally included on the CRFs. These fields provide the site with a pre-defined space to further explain or clarify an associated variable within the CRF. For example, the Adverse Events CRF may include an “Other Action Taken” field which enables recording free text to describe actions taken that are not included in a codelist.

Solicited comments have also previously been collected using a General Comments CRF. Of the companies represented within the CDASH Comments sub-stream, only one company indicated that they continue to collect free text on a General Comments CRF; all others are discontinuing or have discontinued such practices.

2.2 Unsolicited Comments

Unsolicited comments are those comments entered outside of pre-defined fields (also referred to as “marginal” comments as they are often written in margins). These may include marginal CRF comments entered by site staff, written by the subject on patient diaries, or EDC capability to capture comments that are not generally included in any clinical domain. Although such comments may be intended to avoid queries, in practice they often lead to data not being entered into the correct field and cause additional work in the review process.

2.3 Considerations Regarding Usage of a General Comments CRF

The Comments sub-stream decided there should be no mandatory data elements for inclusion in a separate Comments CRF. The sub-stream suggests avoiding the creation of a General Comments CRF. This does not pertain to solicited free-text fields, such as the Adverse Events CRF “Other Action Taken”, that may appear within another established domain.

2.4 Rationale

Clinical data must be entered in appropriate fields; otherwise there is a potential for hidden safety events. For example if an unsolicited general comment of “subject visit was delayed as he had the flu” was captured, this would necessitate that “flu” be entered in the Adverse Event CRF and not left as a comment.

The Comments sub-stream encourages CRF development teams to strive for better data collection methods rather than relying on General Comments CRF. If there is no mechanism for recording general comments (not related to specific data points), it will be incumbent upon teams to design data collection tools capable of capturing all required data for analysis purposes in dedicated fields. The Comments sub-stream suggests that CRF development teams consider what additional information may be needed within a specific CRF. It is better to ask specific questions through creation of well-defined variables that will be more meaningful for analysis rather than inconsistently capturing this information within general comments fields.

General comments are inefficient to program against due to inconsistent wording and frequent misspellings and therefore offer limited or no value for statistical analysis, as they cannot be tabulated. An additional concern is the potential for inappropriate, or sensitive, information to be included within general comments fields. For example, a comment could contain a name or may have unblinding information.

Unsolicited comments which may have been intended to avoid queries, for example "subject visit was delayed due to his holidays", are not regarded as clinical data. The Investigative site or monitor should be trained to enter the contents of the comments in the appropriate field rather than making marginal notes on the CRF. There is a higher time/cost consideration associated with unsolicited comments and they should be discouraged; as they are labor intensive to data-enter, review and act upon.

There does not appear to be an ICH E3 requirement to enter unsolicited comments in the datasets that are submitted to the regulatory parties. The Comments sub-stream consensus is that only the parameters captured in appropriate CRF fields are considered clinical study data that is submitted to regulatory parties in datasets; all other comments are considered unsolicited comments.

Individual sponsor companies must determine their own path in handling the situation should unsolicited comments appear on CRFs.

3. Protocol Deviations CRF

3.1 Protocol Deviations Review

The Protocol Deviations sub-stream reviewed the information gathered, eliminated redundant fields and collapsed fields that were similar – resulting in a wide list of variables relating to Protocol Deviations. The sub-stream then assigned each of the variables to the appropriate category (with corresponding tables) of highly recommended, recommended/optional or not necessary to collect on a CRF.

The sub-stream reviewed the regulatory requirements pertaining to collection of protocol deviation information. While the regulations, such as ICH/E6 GCP 4.5.2, typically spoke to the protocol deviation documentation requirements of the Investigator or Internal Review Board (IRB) and not specifically to collection of the information within a CRF or database, there were some relevant regulations and ICH Guidance documents. The ICH E3: Guidance for Industry: Structure and Content of the Clinical Study, section 10.2, requires the reporting of protocol deviation information "related to study inclusion or exclusion criteria, conduct of the trial, patient managements or patient assessment" within the body of the text and patient data listings. The 21 CFR Part 812, Investigational Device Exemptions also requires documentation of the dates of, and reasons for, deviating from the protocol.

3.2 Considerations Regarding Usage of a Protocol Deviations CRF

Most sub-stream participants emphasized that their companies did not utilize specific CRFs for collection of protocol deviations. This information was derived from other CRF domains or system functionalities. As a result, the Protocol Deviations sub-stream recommends avoiding the creation of a Protocol Deviations CRF.

The sub-stream did, however, develop a CDASH data collection standard for Protocol Deviations that maps to the SDTM DV domain, but did not categorize any of the variables as highly recommended. Table 2 was developed as a guide that clinical teams could use for designing a Protocol Deviations CRF and study database should they choose to do so.

3.3 Rationale

If a sponsor decides to use a Protocol Deviations CRF, the sub-stream felt the sponsor should not rely on this CRF as the only source of protocol deviation information for a study. Rather, they should also utilize

monitoring, data review and programming tools to assess whether there were protocol deviations in the study that may affect the usefulness of the datasets for analysis of efficacy and safety. By utilizing this information a sponsor can then decide which method is best for their company.

4. Table 1: Highly Recommended Data Collection Fields

*There is no table for “Highly Recommended Data Collection Fields” since nothing falls under that category for Protocol Deviations.

5. Table 2: Recommended / Conditional Data Collection Fields

*There is no table for “Highly Recommended Data Collection Fields” since nothing falls under that category for Protocol Deviations.

6. Table 3: Optional Data Collection Variables*

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM Core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
1	Protocol Deviation Term (text)	DVTERM *(required)*		Verbatim text of the variation from processes or procedures defined in a protocol.	Record protocol deviation identified.	This may be derived from clinical data or captured in the clinical data management system.
2	Protocol Deviation Coded Term	DVDECOD *(permissible)*		Controlled terminology for the name of the protocol deviation.	Select appropriate code from list of protocol deviation terms.	May capture this programmatically or manually (manual may be a combination of manual review and programmed coding).
3	Category for Protocol Deviation	DVCAT *(permissible)*		Category of the deviation criteria.	Would not be entered by clinical site.	May be derived by the sponsor. May be sponsor-defined. Example: MAJOR or MINOR.
4	Start Date	DVSTDTC *(permissible)*	DVSTDT *(Note: this is a data collection variable, if collected will be derived into DVSTDTC)*	Start date of the protocol deviation	Record the date that the protocol deviation began using the format of DD/MMM/YYYY. This should be the start or occurrence of the protocol deviation and not the date it was discovered or reported.	This may be derived. SDTM Variable DVSTDTC: Concatenate Start Date and Time (if time is collected) into DVSTDTC using the ISO 8601 format (YYYY-MM-DDTHH:MM:SS).
5	Start Time	DVSTDTC *(permissible)*	DVSTTM *(Note: this is a data collection variable, if collected will be derived into DVSTDTC)*	Start time of the protocol deviation	If appropriate, record the time the protocol deviation began using a 24 hour clock in HH:MM:SS format, as needed. Midnight should be recorded as 00:00:00 and starts the new day. This should be the start or occurrence of the protocol deviation and not the time it was discovered or reported.	This may be derived. May capture date and not time.

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM Core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
6	End Date	DVENDTC *(permissible)*	DVENDT *(Note: this is a data collection variable, if collected will be derived into DVENDTC)*	End date of protocol deviation.	Record the date that the Protocol deviation ended using the format of DD/MMM/YYYY. This should be the date the protocol deviation stopped and not the date it was discovered or reported.	This may be derived. SDTM Variable DVENDTC: Concatenate Start Date and Time (if time is collected) into DVSTDTC using the ISO 8601 format (YYYY-MM-DDTHH:MM:SS).
7	End Time	DVENDTC *(permissible)*	DVENTM *(Note: this is a data collection variable, if collected will be derived into DVENDTC)*	End time of protocol deviation	Optionally, if appropriate, record the time the protocol deviation ended using a 24 hour clock in HH:MM:SS format, as needed. Midnight should be recorded as 00:00:00 and starts the new day. This should be the time the protocol deviation stopped and not the time it was discovered or reported.	This may be derived. May capture date and not time.[same as above]
8	Trial Epoch	EPOCH *(permissible)*		Epoch associated with the start date/time of the protocol deviation.	Record Epoch associated with the start date/time of the protocol deviation. Examples: TREATMENT PHASE, SCREENING and FOLLOW-UP.	May be derived in the analysis dataset.
9	Were there any protocol deviations?	None	DVYN	Indication of whether or not there was a protocol deviation.	Enter "Yes" if a protocol deviation occurs and No if none occur and subject has completed treatment.	May be derived in the analysis dataset.
10	Sponsor-Defined Identifier	DVSPID *(permissible)*	DVSPID	Sponsor-defined reference number	Record the line number if not pre-printed on the CRF.	This may be defined in the sponsor's operational database, such as line number on a CRF page.

* The Protocol Deviations Sub-Stream developed Table 2 as a guide that clinical teams could use for designing a Protocol Deviations CRF and study database should they choose to do so. This also allows for consistent item collection in meeting SDTM requirements.

7. Table 4: Examples of Data Collection Fields Generally Considered Not Necessary to Collect on CRF

	SDTM Submission Variable Name	Variable Label	Definition	Applicable Regulations	Rationale
1	None	Source of Protocol Deviation	Field of reference for protocol deviation or CRF source of protocol deviation.		May be derived, optional for paper-based studies but unnecessary for all others
2	None	CRF Page # of deviation	CRF page number where protocol deviation occurs		May be derived, optional for paper-based studies but unnecessary for all others
3	None	Page sequence number	CRF page number within collection of Protocol Deviations CRF pages		Optional for paper-based studies but unnecessary for all others
4	None	Check if last Page	Check box if this is the last page or protocol deviations		Optional for paper-based studies but unnecessary for all others
5	None	Protocol deviation page _ of _ pages	The number of the specific page of total pages of protocol deviations.		Optional for paper-based studies but unnecessary for all others
6	None	Check if None	Check if no protocol deviations reported.		Chose to utilize other flag variable.
7	None	Was Protocol Deviation approved by sponsor?	Check if protocol deviation was approved by sponsor.		Not considered appropriate for clinical data – particular to another process.
8	None	Approver's Name	Name of staff approving protocol deviation.		Not considered appropriate for clinical data – particular to another process.
9	None	Date of Notification	Date sponsor was notified of protocol deviation.		Not considered appropriate for clinical data – particular to another process.
10	None	Excluded Days			
11	None	Date of Approval	Date protocol deviation was approved.		
12	DOMAIN *(required)*	Domain Abbreviation	Two-character abbreviation for the domain most relevant to the observation for example DV for Protocol Deviation.		Derived.

	SDTM Submission Variable Name	Variable Label	Definition	Applicable Regulations	Rationale
13	USUBJID *(required)*	Unique Subject Identifier	Unique subject identifier within the submission.		Derived.
14	DVSEQ *(required)*	Sequence Number	Sequence number given to ensure uniqueness within a dataset for a subject. Can be used to join related records.		Derived.

Drug Accountability & Exposure

Harmonized Version

Stream Leader: Liz M. Nulton-Bodiford,
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Co-Stream Leader: Melissa Binz, Wyeth

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Section 3. Drug Accountability & Exposure Stream Draft Version

1. Introduction

The Drug Accountability & Exposure work stream has volunteers from pharmaceutical/biotech and software development. The team is comprised of many people with Clinical Trial and Data Management experience. The team also has several programming and standards maintenance representatives and a representative from the United States government.

Team Members	Affiliation	Location
Liz Nulton-Bodiford	GSK	RTP, NC, US
Haritini Leptou	Forest Labs	US
Xingji Han	Novartis Pharma. Corp.	East Hanover, NJ
Roger Duguid	PharmaNet	Cary, NC, US
Marie-Louise Trotman	Amgen	Southern CA, US
Lisa Leubner Cashman	Genzyme Corp.	Cambridge, MA, US
Patty Yost	RTI International	RTP, NC, US
Varia Cartledge,	Biogen	Cambridge, MA
Hermann Ziehl	Schwarz Biosciences	Monheim, Germany
Patricia Burden-Brady	Eli Lilly & Co	Indiana, US
Venky Chakravarthy	Biopharma Data Services	Michigan, US
Moto Nishi, MBA	Astellas Pharma Inc.	Japan
Dagmar Kottig-Roth, PhD	Accovion GmbH	Frankfurt, Germany
Ray Day	NIH Office of Biotechnology Activities	Maryland, US
Cheryl A. Simon	SP Corp	US
Michael Bretschneider	Schwarz Bioscience	Monheim, Germany
Melissa Binz	Wyeth	Collegeville, PA, US
Heather Wolff	Millennium Pharmaceuticals	Cambridge, MA, US
Lisa Pacelli	Bristol-Myers Squibb	US
Patrick Culot	UCB Pharma SA	Belgium
Lorna Griffin	MRL, Merck & Co., Inc.	New Jersey, US
Amy E. Plodek	Boston Scientific	San Jose, CA , US
Tang Li	Cephalon	Frazier, Pennsylvania, US
Shigang Shen	Millennium	Cambridge, Massachusetts, US
Margarita Harrod	Merck	New Jersey, US
Deborah Baretz	Eisai	New Jersey, US

The work stream reviewed sample Case Report Forms (CRFs) which were submitted by Pharmaceutical, Biotechnology firms and Contract Research Organization with the aim of identifying variables which are commonly collected across the industry. This document describes highly recommended, recommended/conditional and optional data variables applicable to CRF design, monitoring and data management of clinical trials which appeared on the sample CRFs that the team reviewed. As a result, there may be additional data variables that would be useful to collect which were not encountered during this analysis.

2. Process

The Streams began by reviewing CRF samples supplied by the Association of Contract Research Organizations (ACRO) and CDASH. Volunteers were asked to collect CRF samples currently in use by industry. Within each Stream, sub-groups were created to scan CRF samples and evaluate their commonalities / differences of the CRF samples.

All of the companies who work with medicinal products are using Case Report Forms (electronic and/or paper) to collect data. Some of the data variables specified below will be part of every CRF across all companies as referenced under "Highly Recommended". However, some will be "Recommended / Conditional" or trial or project specific. While each company collects data in different ways, it is important to remember that this work stream was formed to define data variables which are useful for all CRFs.

The "CDASH CRF Data Collection Field" column contains the proposed text for inclusion on the CRF. The SDTM variables served as a target for deliverable data and all data variables were mapped to the SDTM variables.

2.1 Process Specifics for Drug Accountability

The aim of the CDASH Drug Accountability proposal is to define the variables needed to assess drug accountability for clinical trial subjects. The Drug Accountability variables may be used to calculate the subject's compliance with the investigational product

This proposal includes the Study Data Tabulation Model variables that appear in the SDTM Implementation Guide 3.1.1. DATEST values can be pre-specified on the CRF if the data is collected in a horizontal format.

The inclusion of a Drug Accountability CRF/eCRF is optional. The team recommends that this data collection instrument is not used for single dose studies because the data collected would be of limited value.

2.2 Process Specifics for Drug Exposure

This proposal includes the Study Data Tabulation Model variables that appear in the SDTM Implementation Guide 3.1.1. The SDTM implementation Guide defines the Exposure domain model as follows.

> *"The Exposure domain model records the details of a subject's exposure to protocol-specified study treatment. Study treatment may be any intervention that is prospectively defined as a test material within a study, and is typically but not always supplied to the subject. Examples include but are not limited to placebo, active comparator, and investigational product. Treatments that are not protocol-specified should be recorded in the Concomitant medications (CM) domain."*

3. Data Collection Variables

3.1 Categories

CDASH core team has agreed on the following categories for classifying the data collection variables:

Highly Recommended = A data collection variable that must be on the CRF (e.g., a regulatory requirement.

Recommend / Conditional = A data collection variable that must be collected on the CRF for specific cases (may be recorded elsewhere in the CRF set or from other data collection sources).

Optional = A data collection variable that is available for use if needed (may be

3.2 Relationship between CDASH variables and SDTM variables

The aim of this proposal is to identify the variables that must be collected on the CRF in order to report the data to regulatory agencies using SDTM. The data collection variables are labeled as 'highly recommended', 'recommended/conditional' or 'optional' to indicate whether they must appear on the CRF. The SDTM variables are labeled as required, expected and permissible with regarding to reporting. Exposure presents special problems because there can be such a big gap between the fields collected on the CRF and the fields that must be present in SDTM. Thus, not all of the required SDTM variables are listed as highly recommended for CDASH because in some situations, these variables may be derived. This requires special attention because randomization data can affect these derivations. For Exposure, many variables may be pre-printed on the CRF, rather than providing a data collection field on the CRF. Special consideration must be given regarding what must be collected on the CRF page and what is required and expected for SDTM.

4a. Table 1a: DA: Highly Recommended Data Collection Variables

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH CRF Variable Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsor
1	Investigational Product Dispensed *(highly recommended)*	DAORRES *(expected)*	n/a	Result of the Drug Accountability assessment as originally received or collected. *(example: actual amount)*	Record the actual amount of investigational product dispensed.	For a study with multiple periods or multiple products dispensed, drug accountability should be assessed for each dispensation. In this case, a sequence number or a group ID should be used to tie together a block of related records and to link dispensed product to returned product. *Note: DATEST must be used in concert with DAORRES and DAORRESUE to describe these distinct pieces of data.*
		DATEST *(required)*		Verbatim name, corresponding to the topic variable, of the test or examination used to obtain the drug accountability assessment. *(example: dispensed)*		
2	Units of Investigational Product dispensed *(highly recommended)*	DAORRESU *(permissible)*	n/a	Unit for DAORRES. *(example: tablets)*	Record the units in which the investigational product was dispensed.	Unit of Product dispensed. *(example: tablets)*. The unit will need to be pre-printed on the CRF or a field provided on the CRF to capture it. *Note: DATEST must be used in concert with DAORRES and DAORRESUE to describe these distinct pieces of data.*
		DATEST *(required)*		Verbatim name, corresponding to the topic variable, of the test or examination used to obtain the drug accountability assessment. *(example: dispensed)*		
3	Investigational Product returned *(highly recommended)*	DAORRES *(expected)*	n/a	Result of the Drug Accountability assessment as originally received or collected. *(example: actual amount)*	Record the actual amount of investigational product returned.	Drug accountability should be assessed for each dispensation for a study with multiple periods or multiple products dispensed. A sequence number or a group ID should be used to tie together a block of related records and to link returned product to product dispensed. *Note: DATEST must be used in concert with DAORRES and DAORRESUE to describe these distinct pieces of data.*
		DATEST *(required)*		Verbatim name, corresponding to the topic variable, of the test or examination used to obtain the drug accountability assessment. *(example: returned.)*		
4	Units of Investigational Product returned *(highly recommended)*	DAORRESU *(permissible)*	n/a	Unit for DAORRES. *(example: tablets)*	Record the formulation or units of investigational product returned.	Unit of Investigational Product returned. *(example: tablets)*. The unit will need to be pre-printed on the CRF or a field provided on the CRF to capture it *Note: DATEST must be used in concert with DAORRES and DAORRESUE to describe these distinct pieces of data.*
		DATEST *(required)*		Verbatim name, corresponding to the topic variable, of the test or examination used to obtain the drug accountability assessment. *(example: returned.)*		

4b. Table 2a: DA: Recommended / Conditional and Optional Data Collection Variables

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsor
5	Date Investigational Product dispensed *(optional)*	DADTC *(Expected)*	n/a	Date of Drug Accountability Assessment	Record the exact date the investigational product was dispensed, using the "DD-MMM-YYYY" format.	The date investigational product dispensed should be recorded for each dispensation for a study with multiple periods or multiple products dispensed.
6	Date Investigational Product returned *(optional)*	DADTC *(Expected)*	n/a	Date of Drug Accountability Assessment	Record the exact date the investigational product was returned, using the "DD-MMM-YYYY" format.	The date investigational product returned should be recorded for each dispensation for a study with multiple periods or multiple products dispensed. If there is only one drug which was dispensed on one occasion, the collection of this data is not applicable.
7	Investigational Product category (examples: study medication, rescue medication) *(optional)*	DACAT *(Expected)*	n/a	Used to define a categorization level for a group of related records.	Record the type of investigational product dispensed/returned. (examples: Study Medication, Comparator, Placebo)	Examples: study medication, rescue medication
8	Investigational Product sub-category (examples: Drug A, Drug B, Rescue) *(optional)*	DASCAT *(permissible)*	n/a	Used to define a further categorization level for a group of related records.	Record the name of the investigational product dispensed/returned. (examples: Drug A, Drug B, Placebo)	

5a. Table 1b: EX: Highly Recommended Data Collection Variables

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
1	Start Date *(highly recommended)*	EXSTDTC *(required)*	n/a	Start date/time of treatment	Please record the exact date of investigational product administration using the "DD-MMM-YYYY" format.	Date when investigational product 'constant dosing interval' started.

5b. Table 2b: EX: Conditional / Optional Data Collection Variables

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
2	Stop Date *(highly recommended / conditional)*	EXENDTC *(permissible)*	n/a	End date/time of treatment	Record the stop date or last date of administration of investigational product using the "DD-MMM-YYYY" format.	Date when investigational product period stopped. If start date and stop date are not expected to be on the same date, the stop date is required. If the trial design indicates that the start and stop date are on the same day, the stop date is not required since it can be assigned to be equal to the start date.
3	Dose Amount *(highly recommended / conditional)*	EXDOSE *(expected)*	n/a	Dose per Administration	Dose or amount of investigational product that was administered to/taken by the subject in the period recorded.	Dose or amount taken per 'constant dosing interval' recorded. Capture of dose is conditional because it may be possible to obtain dose by other methods (e.g. derived from randomization data).
4	Dose Unit *(highly recommended / conditional)*	EXDOSU *(expected)*	n/a	Units for EXDOSE and EXDOSTOT. (Examples: ng, mg, or mg/kg.)	Unit of dose or amount taken per period recorded.	Unit of dose or amount taken per 'constant dosing interval' recorded. Capture of dose unit is conditional because it may be possible to obtain dose by other methods (e.g. derived from randomization data). The unit will need to be pre-printed on the CRF or a field provided on the CRF to capture it.
5	Investigational Product Identification Number *(optional)*	EXLOT Or EXSPID (either can store IP ID number) *(permissible)*	n/a	EXLOT = Lot Number of the EXTRT product. EXSPID = Sponsor defined reference number. Perhaps pre-printed on the CRF as an explicit line identifier or defined in the sponsor's operational database.	Reference number that appears on the container holding the investigational product e.g. Lot Number	Reference number that appears on the container holding the investigational product. Investigational Product Identification Number is a unique number, which provides mapping to Lot Number and possibly the randomization schema.

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
6	Investigational Product Name *(optional)*	EXTRT *(required)*	n/a	Name of the intervention treatment — usually the verbatim name of the investigational treatment given during the 'constant dosing interval' for the observation.	Name of investigational product.	Name of investigational product that was administered to the subject. This must be collected if it cannot be derived. Field must always be present on the underlying database.
7	Start Time *(optional)*	EXSTDTC *(date required – time is a level of specificity)*	n/a	Start date/time of treatment.	Time when administration of investigational product started.	Time when investigational product period started.
8	Stop Time *(optional)*	EXENDTC *(permissible)*	n/a	End date/time of treatment	Time when investigational product administration stopped e.g. for infusions this is the time when the infusion ended.	Time when investigational product 'constant dosing interval' ended/stopped.
9	Dose Adjusted? Yes/No (*optional)*	(SUPPQUAL)	EXDOSADJ	n/a	Select either Yes or No to indicate whether there was a change in dosing.	Will provide a definitive response regarding dose changes.
10	Reason for Dose Adjustment (*optional)*	EXADJ (*permissible)*	n/a	Describes reason or explanation of why a dose is adjusted – used only when an adjustment is represented in EX. May be used for variations from protocol-specified doses, or changes from expected doses.	If there was a change in dosing, record the reason for change.	Captures reason dose was changed / modified. The reason may be chosen from a select list or entered as free text.
11	Frequency *(optional)*	EXDOSFRQ *(permissible)*	n/a	Usually expressed as the number of dosings given per a specific interval. Examples: BID, QID.	Indicate the frequency the investigational product was administered for a defined period of time.	Number of doses given per a specific interval.
12	Route *(optional)*	EXROUTE *(permissible)*	n/a	Route of administration for EXTRT. Examples: ORAL, INTRAVENOUS.	Record the route of administration e.g. iv, oral or transdermal or enter the appropriate code from the code list.	Route of investigational product administration. This will often be pre-printed on the CRF. If it is not pre-printed, a field will need to be provided on the CRF.

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
13	Formulation *(optional)*	EXDOSFRM *(required)*	n/a	Dose form for EXTRT. Examples: TABLET, LOTION.	Record the formulation e.g. infusion, solution, tablet or enter the appropriate code from the code list.	Formulation of investigational product. This must be collected if it can not be derived. Field must always be present on the underlying database.
14	Duration of Interruption (including units) *(optional)*	*(SUPPQUAL)*	EXDURITP	n/a.	Specify the duration of treatment interruption.	Duration of treatment interruption. In some situations, the duration of the interruption may be calculated from the administration start and stop times recorded elsewhere in the CRF.
		This will need to be mapped to a SDTM supplemental qualifier if it needs to be reported.		n/a	Unit (i.e. minutes, hours, days) for the duration of treatment interruption.	The unit (i.e. minutes, hours, days) needs to be collected as a qualifier to the number for duration.
15	Body Location *(optional)*	EXLOC *(permissible)*	n/a	Specifies anatomical location of administration Example: LEFT ARM for a topical application.	Body location where the investigational product was administered e.g. shoulder, hip, arm.	Location where the investigational product was administered. This may be pre-printed or collected.
16	Total volume prepared *(optional)*	(SUPPQUAL)	EXTVLPR	n/a	Total volume prepared, e.g. volume of the carrier solution plus volume of the investigational product solution.	Total volume prepared, e.g. volume of the infusion.
17	Total volume prepared unit *(optional)*	(SUPPQUAL)	EXTVLPRU	n/a	Unit of the prepared volume e.g. mL.	Unit of the prepared infusion volume e.g. mL.
18	Total volume infused *(optional)*	(SUPPQUAL)	EXVAMT	Exposure volume amount	Record the total volume that was administered/given to the subject.	Infusion volume that was given to the subject.

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM core)*	CDASH Data Collection Field Name	Definition	Instructions to Clinical Site	Implementation / Rationale for Sponsors
19	Total volume infused unit *(optional)*	(SUPPQUAL)	EXVAMTU	Exposure volume amount units	Unit of total volume administered / given to the subject e.g. mL	Unit of the infusion volume e.g. mL.
20	Flow Rate *(optional)*	(SUPPQUAL)	EXFLRT	n/a	Rate of Infusion e.g. 10 mL/min. Record "10"as the infusion rate	Infusion rate. This can be used to derive dose.
21	Flow Rate Unit *(optional)*	(SUPPQUAL)	EXFLRTU	n/a	Record the unit for the infusion rate eg. mL/min	Unit of the infusion rate e.g. mL/min.
22	Dose Administered? Yes/No *(optional)*	EXOCCUR *Note: the inclusion of EXOCCUR in SDTM is still under discussion by the SDS team. This may need to be revisited.*	n/a	n/a	Select either Yes or No to indicate whether subject has taken the dose of investigational product.	Indicates that the subject did/did not receive a dose of investigational product.
23	Planned Timepoint *(optional)*	EXTPT (permissible)	n/a	Planned timepoint name	Indicates the planned timepoint of investigational product administration e.g. morning / evening.	Indicates the planned timepoint of investigational product administration, e.g. morning / evening.
24	Gauge of needle used to administer investigational product *(optional)*	(SUPPQUAL)	EXGAUG	n/a	Indicates the needle gauge used for the injection of investigational product.	Needle gauge used for the injection of investigational product.
25	Did subject complete full course of study med? *(optional)*	(SUPPQUAL)	EXMEDCMP	n/a	Select either Yes or No to indicate whether subject has completed the full course of treatment.	Depending on how the investigational product details are collected via the CRF/eCRF, it may be possible to derive this data.

6a. Table 3a: DA: Data Collection Variables Considered Not Necessary to Collect on CRF

Definition	Recommendation	Rationale
Capsules actually taken	If needed, it can be derived based on Dispensed less Returned.	This may be covered by one of the DATESTCD values.
Was study medication dispensed during the study?	Not needed	This question was present on an electronic data capture screen for navigation purposes. This data can be derived from other sources.
Was study medication taken during the study?	Not needed	This question was present on an electronic data capture screen for navigation purposes. This data can be derived from other sources.
Was the study medication dose modified during the study?	Not needed	This question was present on an electronic data capture screen for navigation purposes. This data can be derived from other sources.
Did subject receive correct treatment? If no, explain	Derivable from other data.	This information will probably be obtained from reviewing the site's drug accountability logs and/or randomization records post-blinding. It may not be possible to answer this question on the CRF prior to breaking the blind.
Was correct treatment delivered?	Derivable from other data.	This information will probably be obtained from reviewing the site's drug accountability logs and/or randomization records post-blinding. It may not be possible to answer this question on the CRF prior to breaking the blind.

6b. Table 3b: EX: Data Collection Variables Considered Not Necessary to Collect on CRF

There were numerous other fields represented in the example CRFs provided by the volunteers. Below is a list of those items that were determined to be 'Unnecessary to Collect' (do not include):

Description	Recommendation	Rationale
Body Surface Area	VS	This is not exposure data, even though it's related to dosage.
Actual Body Weight	VS	This is not exposure data, even though it's related to dosage.
Was any sedation or topical anesthetic given?	CONMED	This is not exposure data, even though it occurs around the time of dose
Weight used to prepare infusion	VS	This is not exposure data, even though it's related to dosage.
Any premeds given?	CONMED	This is not exposure data, even though it occurs around the time of dose.
Total input / output amounts and types (PRBC, Enteral nutrition, prenteral nutrition, conmed, other / Other blood loss including drainage, other)	CONMED	Not exposure data
Date of Dose Change	Not needed	Derivable from start date field provided that a new record is recorded in the database when the dose changes
AE # associated with Dose Change	Not needed	Administrative field that is not necessary on CRF.
Was entire dose administered?	Not needed	Derivable from protocol specifications and dose/amount taken
Did subject receive at least one dose?	Not needed	Derivable from other data
Was the dose stopped early?	Not needed	Derivable from other data

7. Other issues related to Exposure and Drug Accountability

The following regulations are applicable to the collection of Exposure and Drug Accountability data:

- ICH E6 Section 4.6.3
- ICH M5 EWG
- ICH E3 Section 12.1

Disposition / End of Study

Harmonized Version

Stream Leader: Alec Vardy

Table of Contents

Section 4. Disposition / End of Study Stream Harmonized Version

1. Introduction and Background

1.1 Introduction

The Disposition / End of Study stream was comprised of 43 members from the pharmaceutical, biotechnology, and medical device industries as well as CROs and academia. Participants hold positions in Clinical Data Management, Clinical Data Standards, Clinical Programming, Biostatistics, Clinical Data Systems, Clinical Research, and Medical Writing. A list of participants and their affiliation is provided in the attachment.

The work stream was divided into four subgroups that worked in parallel. A coordinating committee met weekly to consolidate discussion, feedback and consensus from the four groups.

1.2 Background

Sample Case Report Forms (CRFs) submitted by the members of this stream were reviewed to identify data collection fields to appear on a Disposition CRF. Completion of study epochs (trial cycles, phases, end of study, etc.) data collection fields were identified as mandatory, conditional, optional or not needed (could or should be captured elsewhere in the CRF). Where applicable, the fields where aligned with the SDTM Disposition (DS) domain fields.

The stream took as its remit the extensive consideration of only disposition events, but was also requested to consider protocol milestones. We note that the DS domain allows for the documentation (and submission) of the completion of protocol milestones (e.g. informed consent obtained, randomized). The stream has not considered the specification of CRF questions (or "mini CRF modules") to capture this information, but accepts that such questions may be included in appropriate places in the CRF (e.g. the date of informed consent is typically collected on the same CRF page as demography data but is mapped for submission to the DS domain) for those sponsors who desire to formally document the completion of protocol milestones.

The stream held extensive discussions around the vocabulary to be used in a controlled terminology list for 'Reason for discontinuation', basing these discussions on the list already published by the CDISC Terminology group. The stream will continue to work to agree upon recommendations to be discussed at a later date with the Terminology group (see also Note 6.iv below).

2. Table 1: Highly Recommended Data Collection Fields

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM Core)*	CDASH Data Collection Field Name	Definition	Applicable Regulations	Instruction to Clinical Site	Implementation / Rationale
1	Subject Status	DSDECOD *(required)* **and** DSTERM *(required)*		Standardized Disposition Term **and** Reported term for the Disposition Event of the subject at a selected trial epoch	Code of Federal Regulations (CFR), Title 21, Chapter I, Subchapter D, Part 312, Subpart B, Section 312.33 Annual Reports (1) International Conference on Harmonization (ICH) Guidance for Industry E6, Good Clinical Practice (2) International Conference on Harmonization (ICH) Guideline for Industry E3, Structure and Content of Clinical Study Reports (3) FDA Guidance for Industry, Premarketing Risk Assessment, March 2005 (4)	Document the subject's status at <insert text corresponding to the selected trial epoch>. If the subject discontinued prematurely, record the primary reason for discontinuation.	See Notes 6.i - 6.v

(1) Section (a) (2) requires the inclusion of "The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason."

(2) Section 4.3.4 states: "Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason (s), while fully respecting the subject's rights.

Section 5.18.4 (m) (v) specifies that the monitor should verify that: "All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs."

(3) Section 10.1 states: "The number of patients who were randomized, and who entered and completed each phase of the study … should be provided, as well as the reasons for all postrandomization discontinuations, grouped by treatment and by major reason (e.g. lost to follow-up, adverse event, poor compliance)."

(4) Section IV.B states "Ascertainment and evaluation of the reasons for leaving assigned therapy during study (deaths and dropouts for any reason) are particularly important for a full understanding of a product's safety profile."

Section VI.F states: "Sponsors should try to ascertain what precipitated dropout or withdrawal in all cases, particularly if a safety issue was a part of the reason for withdrawal. It is not helpful to simply record vague explanations such as 'withdrew consent', 'failed to return', 'administratively withdrawn', or 'lost to follow-up.'", and "Patients considering withdrawing consent should be encouraged to provide the reason, and patients who withdraw should be encouraged to provide information as to whether the withdrawal of consent resulted from a serious or significant safety issue"

3. Table 2: Recommended / Conditional Data Collection Fields

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM Core)*	CDASH Data Collection Field Name	Definition	Applicable Regulations	Instruction to Clinical Site	Implementation / Rationale
1	Trial Epoch	EPOCH *(permissible)*		Trial epoch (trial cycle, phase, end of study, etc.) for which subject disposition is being collected		(Typically, the trial epoch will be pre-printed on the CRF as the title of the page; however, for those companies whose standard CRF module includes a "pick-list" of epochs, the following instruction is given) Check the <*epoch, or insert more appropriate wording*> for which disposition is being recorded	Typically, the trial epoch will be pre-printed on the CRF as the title of the page; however, some companies have a standard CRF module that includes a "pick-list" of epochs
2	Date of Completion or Discontinuation	DSSTDTC *(expected)*		The date that the subject completed the selected trial epoch, or the date that the subject discontinued from the selected trial epoch	Not applicable	Record the date that the subject completed the selected trial epoch as defined in the protocol and/or CRF Completion Instructions. If the subject did not complete the selected trial epoch, record the date that they discontinued to the best of your knowledge.	Define in the protocol and/or CRF Completion Instructions the criteria for completion of each trial epoch for which a disposition CRF will be provided Only collect the date of completion or discontinuation on the disposition CRF module if the same information is not being collected on another CRF module. For example, if the date of the last dose is defined to mark the end of the Treatment Phase epoch, and is collected on the Drug Exposure form, then this field would not be collected on the Disposition CRF module.

4. Table 3: Optional Data Collection Fields

	CDASH CRF Data Collection Field	SDTM Submission Variable Name *(SDTM Core)*	CDASH Data Collection Field Name	Definition	Applicable Regulations	Instruction to Clinical Site	Implementation / Rationale
1	Will the subject continue ?	Not applicable	DSCONT	Plan for subject continuation to the next phase of the trial or another related trial at the time of completion of the CRF	Not applicable	To the best of your knowledge, record if the subject will be continuing to the next phase of this trial or another related trial? *(Sponsor should specify what the next phase of the trial or the related trial is)*	
2	Next trial epoch or new trial subject will be entering	Not applicable	DSNEXT	Identifies the trial epoch or new trial in which the subject will participate	Not applicable	Record the trial epoch or trial identifier if the subject is continuing.	
3	Was treatment unblended by the site?		DSUNBLND	Identifies in a blinded trial whether or not the subject's blind was broken by the site	ICH E.3, Section 10.1	Was the subject's treatment assignment unblended by the site?	

5. Table 4: Examples of Data Collection Fields Generally Considered Not Necessary to Collect on CRF module

	SDTM Submission Variable Name *(SDTM Core)*	Variable Label	Definition	Applicable Regulations	Rationale
1	DSSEQ *(required)*	Sequence Number	Sequence number given to ensure uniqueness within a dataset for a subject. Can be used to join related records.		Derived.
2	DSGRPID *(permissible)*	Group ID	Used to tie together a block of related records in a single domain to support relationships within the domain and between domains.		Not needed.
3	DSREFID *(permissible)*	Reference ID	Optional internal or external identifier.		Not needed.
4	DSSPID *(permissible)*	Sponsor-Defined Identifier	Optional Sponsor-defined reference number. Perhaps pre-printed on the CRF as an explicit line identifier or defined in the sponsor's operational database. Example: Line number on a Disposition page.		Not needed.
5	DSCAT *(permissible)*	Category for Disposition Event	Used to define a category of related records. Examples: DISPOSITION EVENT or PROTOCOL MILESTONE		Derived.
6	DSSCAT *(permissible)*	Subcategory for Disposition Event	A further categorization of disposition event.		Not needed.
7	DSDTC (*permitted)*	Date/Time of Collection	The date that the disposition of the subject was collected	None	Not needed since the date of interest is the actual date of completion or discontinuation
8	DSSTDY *(permissible)*	Study Day of Start of Disposition Event	Study day of start of the disposition event relative to the sponsor-defined RFSTDTC.		Derived if needed.
9		Death details	Information such as Date of Death (if not the disposition event for a specified trial epoch and/or if required for every subject in order that a survival analysis can be performed), Cause of Death (if not requested on disposition CRF), whether autopsy done, etc.		This information is not strictly required for the description of subject disposition; if required, it should be collected on a separate CRF module. A Clinical Events module is proposed by the SDS team in the draft SDTM Implementation Guide that could be used to submit such data

	SDTM Submission Variable Name *(SDTM Core)*	Variable Label	Definition	Applicable Regulations	Rationale
10		Follow-up / vitals information	Information such as method of contact, frequency of contact attempts, whether subject is dead or alive, etc.		This information is not strictly required for the description of subject disposition; if required, it should be collected on a separate CRF module
11		Additional blind break information (see also Table 3, Item 3	Information such as when blind was broken, reason for blind break, treatment administered to subject, etc.		This information is not strictly required for the description of subject disposition; if required, it should be collected on a separate CRF module
12		Date of Withdrawal of Consent	The date on which consent was withdrawn		Considered redundant field when date of completion or discontinuation is collected
13		Comments	Open comment field		Any additional information should be recorded as a specification of the reason for discontinuation

6. Notes

i. Collecting a single field (as opposed to a "Yes/No" question asking whether the subject completed followed by a question to determine the reason for discontinuation for those subjects who failed to complete) to document final status:

- Eliminates the need for reconciliation between the "Yes/No" question and the reason for discontinuation
- Simplifies data collection
- Permits an identical method of collection for each protocol milestone where status is to be documented

ii. In considering the option "Completed":

- "Completed" may be omitted if completion is not possible due to study design
- "Completed" should be clearly defined either on the CRF or in CRF Completion Instructions (in the latter case, preferably on the facing page to the CRF (for paper CRFs), or in a pop-up window on the screen (for electronic CRFs)); "Completed" should be defined in the protocol, or the definition provided in the CRF or CRF Completion Instructions must be consistent with the contents of the protocol
- "Completed" should be separated from the other terms (reasons for non-completion) in the CRF lay-out in order to re-emphasize its importance

iii. Requesting a single (primary) reason for non-completion (as opposed to multiple reasons) is in line with the ICH Guideline E3 Section 10.1, which states: "there should be a clear accounting of … the reasons for all post-randomisation discontinuations, grouped by treatment and by major reason."

iv. Controlled terminology:

- The current controlled terminology list includes: Adverse Event, Completed, Death, Lack of efficacy, Lost to follow-up, Non-compliance with study drug, Other, Physician decision, Pregnancy, Progressive disease, Protocol violation, Recovery, Screen failure, Study terminated by sponsor, Technical problems, and Withdrawal by subject. **Discussions with the CDISC Terminology group will take place to confirm that the list is complete and accurate; the stream will agree upon proposals prior to this discussion.**
- **The stream strongly recommends that the controlled terminology list, once confirmed, should be made non-extensible. Our concern is that an extensible list might be used in such a fashion as to impair the ability to aggregate data from different sponsors.**
- The Subject Status data collection field will be presented on the CRF as a check box linked to an item from the approved controlled terminology list (DSDECOD)
- For those companies that wish to collect sponsor- and/or study-specific reasons for discontinuation (DSTERM), the stream recommends that these reasons be pre-printed on the CRF, with check boxes for completion wherever possible, as sub-categories of the appropriate DSDECOD item. **The stream will propose mappings of the more common sponsor- and study-specific reasons after its discussions with the CDISC Terminology group; the stream strongly recommends limiting the use of sponsor- and study-specific reasons in order to promote consistent use of terminology and hence permit the combination of data across multiple sponsors.**
- In some circumstances (e.g. DSDECOD = "Withdrawal by subject" or "Other"), where additional information may be valuable but where it may not be possible to specify sub-categories explicitly, "specify" lines may be inserted next to the appropriate controlled terminology items to permit this information to be collected. This is in line with the FDA Guidance on Premarketing Risk Assessment, which states that "It is not helpful to simply record vague explanations such as 'withdrew consent', 'failed to return', 'administratively withdrawn', or 'lost to follow-up.'", and "Patients considering withdrawing consent should be encouraged to provide the reason, and patients who withdraw should be encouraged to provide information as to whether the withdrawal of consent resulted from a serious or significant safety issue"

- The controlled terminology list may be filtered to omit terms that are not applicable for a study or particular milestone.

v. Protocol milestones:

- The current controlled terminology list allows for the documentation (and submission) of the completion of protocol milestones (e.g. informed consent obtained, randomized)
- This stream has not devoted any time or effort to the specification of CRF questions (or "mini CRF modules") to capture this information, but accepts that such questions may be included in appropriate places in the CRF (e.g. the date of informed consent is typically collected on the same CRF page as demography data but is mapped for submission to the DS domain) for those sponsors who desire to formally document the completion of protocol milestones.

Section 5. Appendices

Appendix 1 Project Background

The Clinical Data Acquisition Standards Harmonization (CDASH) project is addressing FDA's Critical Path Opportunity (#45) whose purpose is to facilitate standardized collection of clinical research data at investigative sites.

#45 Consensus on Standards for Case Report Forms. *Clinical trial data collection, analysis, and submission can be inefficient and unnecessarily expensive. A wide array of different forms and formats are used to collect clinical trial information, and most data are submitted to the FDA on paper. Differences in case report forms across sponsors and trials creates opportunities for confusion and error. Standardization of the look and feel of case report forms could reduce these inefficiencies and also help accelerate progress toward electronic data capture and submission. (Critical Path Opportunities List (Innovation/Stagnation) link: http://www.fda.gov/oc/initiatives/criticalpath/opportunities06.html)*

Standards can substantially reduce time and resource needs for clinical research studies, particularly when they are implemented in the start-up stage. (*Applied Clinical Trials, June 2007*). In addition, they have been reported to improve project team communication and resulting data quality.

Through standardization of basic data collection fields, efficiencies can be achieved that will result in less confusion across sponsors, investigators and research sites and will require less data cleaning and facilitate more efficient monitoring, audit, submission and review procedures.

The CDASH project continues the CRF standardization work initiated by the Association of Clinical Research Organizations (ACRO). It was recommended that CDISC take the leadership role during the January 2006 - DIA Open Forum "Creating Clinical Trial Efficiencies through Standard Data Collection" organized by CDISC, FDA, ACRO. CDISC has expertise in standards development demonstrated by former CDISC work, such as in the development of the Study Data Tabulation Model (SDTM) for reporting results in regulatory submissions to FDA, can be leveraged in the CDASH project.

In June 2006 the initial Collaborative Group was announced by Dr. Woodcock at the Annual DIA Meeting in Philadelphia "Human Subject Protection/Bioresearch Monitoring Initiative and Critical Path Update".

CDASH strategy and resources are the responsibility of the Collaborative Group, which is comprised of the following organizations:

- American Medical Informatics Association (AMIA)
- Association of Clinical Research Organizations (ACRO)
- Association of Clinical Research Professionals (ACRP)
- Baylor College of Medicine
- Biotechnology Industry Organization (BIO)
- Clinical Data Interchange Standards Consortium (CDISC)
- Clinical Research Forum
- Critical Path Institute
- Duke Clinical Research Institute (DCRI)
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
    - The Clinical Research Policy Analysis and Coordination Program
    - The National Cancer Institute (NCI)
        - NCI-Cancer Bioinformatics Grid (caBIG)
        - NCI-Enterprise Vocabulary Service (EVS)

- The National Clinical Research Resources (NCRR)
- The National Institute of Child Health and Human Development (NICHD)
- The National Library of Medicine (NLM)

- Pharmaceutical Research and Manufacturers Association (PhRMA)
- Society for Clinical Data Management (SCDM)

A CDISC Project Kick-off meeting was held in October 2006 to initiate the first CDASH three project work streams (sub-groups).

The primary goal of the CDASH project is the development of a set of 'content standards' for a basic set of global data collection fields that will support clinical research studies. These "content standards" consist of:

- Data Collection Fields
- Definitions
- Site Completion Instructions
- Implementation / Rationale

for a basic set of global data collection fields that will support clinical research studies.

The initial scope of the project is the development of 16 CRF content 'safety data/domains'

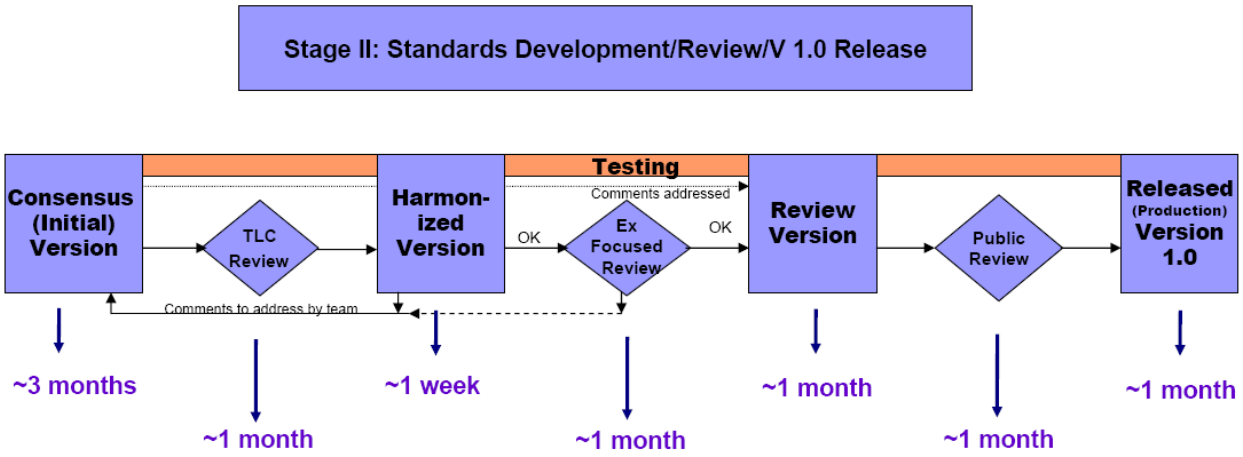
Domains	
Adverse Events (AE)	Inclusion and Exclusion Criteria (IE)
Concomitant Medications (CM)	Lab (LB)
Comments (CO)	Medical History (MH)
Demographics (DM)	Physical Examination (PE)
Disposition (DS)	Protocol Violations (DV)
Drug Accountability (DA)	Subject Characteristics (SC)
ECG (EG)	Substance Use (SU)
Exposure (EX)	Vital Signs (VS)

These safety domains are common to all therapeutic areas. The initial scope is on CRF content not the physical layout of CRFs. Terminology is out of scope for the CDASH work streams; rather, terminology is incorporated through collaboration with the CDISC Terminology Team.

Basic data collection fields identified by CDASH project work streams (via the CDISC consensus process) are mapped into the Study Data Tabulated Model (SDTM) and are compliant with the SDTM Implementation Guide (SDTM IG). SDTM "required" data collection fields have been addressed in the CDASH recommendations.

Appendix 2 Project Process

The CDASH Project follows the CDISC Operating Procedure (COP-001) for Standards Development (http://www.cdisc.org/about/bylaws_pdfs/CDISC-COP-001-StandardsDevelopment-Feb2006.pdf). Following is flow diagram that describing the Stage II: Standards Development/Revision/Release of Version 1.0.



The CDISC Standards Development Process calls for a minimum of three reviews to build consensus towards the Version 1.0 standard (see section 2.0). The CDASH domain-specific recommendations from the workstreams are first reviewed by an internal CDISC Technical Leadership Committee (TLC) to ensure that they do not diverge from the other relevant CDISC standards. They are then combined into 'review packages' for external review by the Collaborative Group, an external focus group in the case of this Project. The entire set of domains will be reviewed together in an open public review process.

To develop the Harmonized Version (HV), the CDISC SDTM variable tables served as a starting/reference point. The CDASH and SDTM variables may differ in certain cases, however, because SDTM is a standard for standardizing results for regulatory submissions whereas CDASH variables are used in the collection of data. Another difference is that the CDASH project is designed to encourage collection of a minimal or basic set of required and necessary data fields whereas SDTM represents more of a 'superset' of variables for reporting results.

In addition to referring to the CDISC SDTM standard, CDASH volunteers were asked to collect CRF samples currently used by industry and to evaluate commonalities and/or differences of CRF samples and the SDTM standard. Workstreams were also asked to document data points that they recommended be including or excluding in the CDASH domains, along with their justifications for these decisions.

2.1 Guiding Principles

The following *Guiding principles were provided to the workstreams in developing their domains. Variables should –

- Ensure that SDTM "required" elements are addressed directly or indirectly
- Be "standard" yet flexible to allow customization within defined limits
- Limit fields to required and necessary
- Comply with regulatory requirements
- Reduce redundancies; not duplicate information found elsewhere in CRFs
- Increase collection of meaningful data
- Facilitate use of standards by all users
- Be appropriate for use in both pre- and post- approval studies
- Allow consistent and efficient data collection/storage/transmission and analysis

**ACRO presentation: 2006-10-18 CDASH Kick-off Meeting*

2.2 Volunteers: Work Streams and Work Stream Procedures

The CDASH project work is performed primarily by volunteers, who are representing biopharmaceutical companies, contract research organizations, academia and government. Each work stream is responsible for one or more domains.

The CDASH Core Team, a qualified, multidisciplinary team of 10 members, leads each of the safety domain work stream listed above. The following table lists the members of the CDASH Core Team and their respective work streams (domains). The Core Team executes the project plan, holding regular conference calls and face-to-face meetings, as appropriate, to achieve the objectives. Each Core Team member led one or more work streams (or sub-group) of volunteer participants. Volunteers for each work stream were recruited via open invitation. Effort was made to ensure that representation on each work stream was from diverse companies, with various functional areas represented and that there was multinational representation whenever possible.

Work streams volunteers were recruited, and there were typically resulting in 10-40 members per workstreams. An effort was made to ensure that there were various functional areas represented and that there was multinational representation whenever possible.

Work stream volunteers were asked to agree on basic data collection fields, map these fields to SDTM, to add definitions and to write instructions for investigative sites and to write implementation guidelines /rationales for study sponsors.

The work streams began by reviewing CRF samples supplied by ACRO (where available), as well as other CRF samples collected that are currently used by industry. Within each work stream, sub-groups were assigned and given the action items of scanning CRF samples and quality control (QC) of CRF examples and establishing the administrative procedures for the workstreams. Weekly or bi-weekly teleconferences provided a communication forum to review and discuss the identification of basic data collection fields for a given domain.

The workstreams collected feedback from numerous functional areas within their respective companies (including ex-US affiliates) to identify the purpose for their respective workstreams' data collection focus (i.e., their domain). The workstreams then focused the group discussions per the Guiding Principles (listed above). For each variable, a category was assigned (highly recommended/recommended/optional, variable labels and definitions were developed. The SDTM submission fields served as a target for deliverable data. Data collection fields were mapped to the SDTM variables as applicable.

Appendix 3 Categories / Designations for Basic Data Collection Fields

In order to facilitate classification of the different types of data collection fields, the following categories were used:

Highly Recommended = A data collection field that should be on the CRF (e.g., a regulatory requirement (if applicable)).

Recommended/Conditional = A data collection field that should be collected on the CRF for specific cases (may be recorded elsewhere in the CRF or from other data collection sources).

Optional = A data collection fields that is available for use if needed (may be recorded elsewhere in the CRF or from other data collection sources).

Highly recommended and recommended/conditional data collection fields are expected to be present on the majority of CRFs, however, it is assumed that sponsors will determine which data fields will be collected based on TA specific data requirements, protocol and other considerations.

It is strongly recommended that standards are defined on the sponsor level taking into consideration the requirements of the stage of clinical development, the individual therapeutic area requirements and NOT on a trial-by-trial basis within the sponsor organization.

The SDTM core designation reflects the expectation of inclusion in an SDTM submission. As an aide to reviewers, SDTM Core Variables***** (Required, Expected and Permissible) are included in the CDASH tables. See the CDISC SDTM Implementation Guide: Human Clinical Trials (Version 3.1.2)

Appendix 4 Explanation of Table Headers

Following are explanations for column headers used in the tables:

CRF Data Collection Field – Provides descriptive text on the type of data to be collected on the CRF.

SDTM Variable Name – Lists the SDTM conforming variable name defined in the SDTM IG along with the SDTM "Core" designation.

CDASH Variable Name - This column provides suggested data collection field names (e.g. CMONG and CMTTM). These variable names are "SDTM-like variables" and can be used as a tool for deriving the SDTM variable needed for reporting.

Definition – Describes the purpose of the data collection field. The text may or may not mirror the text in the SDTM IG (under variable label or CDISC notes).

Instructions to Clinical Site –Contains information for the clinical site on how to enter collected information onto the CRF.

Implementation Guidelines –Contains further information on how to implement the CRF data collection fields.

Note: "Instructions for the Clinical Site" and "Implementation Guidelines" are provided only for those data collection fields that are considered "highly recommended" and "recommended/optional".

Appendix 5 Core Team and Stream Members

Core Team			
Work stream Leader	**Affiliation**	**Email address**	**Stream**
Rhonda Facile	CDISC	rfacile@cdisc.org	Project Director
Paul Bukoweic	Millennium Pharmaceuticals	Paul.Bukoweic@mpi.com	Physical Exam & Vital Signs
Dorothy Dorotheo	Intermune	DDorotheo@intermune.com	Concomitant Medications
Shannon Labout	CSS Informatics and SCDM	shannon.labout@csscomp.net	Inclusion/Exclusion
Jay Leeka	AstraZeneca	Jay.Leeka@astrazeneca.com	Comments & Protocol Deviations
Liz Nulton-Bodiford	GlaxoSmithKline	liz.m.nulton-bodiford@gsk.com	Drug Accountability & Exposure
Trisha D. Simpson	Schwarz BioSciences/UCB	Trisha.Simpson@ucg-group.com	Medical History & Substance Use
David Tatum	Eli Lilly & Co./Consultant	tatum4@comcast.net	Adverse Events
Kim Truett	KCT Data, Inc.	Kim.Truett@kctdm.com	Lab
Alec Vardy	CV Therapeutics/Consultant	Alec.Vardy@cvt.com	Disposition/ End of Study
Gary Walker	Quintiles	gary.walker@quintiles.com	Demographics & Subject Characteristics and ECG

Stream Members *(to add later – alpha by company name)*

Stream Members		
Organization	**Name**	**Stream(s)**

Appendix 6 Revision History

None.

Appendix 7 Place holder for IP

Representation and Warranties; Limitations of Liability, and Disclaimers