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CDISC
Setting the Global Standard for Clinical Data

CDISC Italian User Group 2009

CDISC Guidelines for Annotating CRFs

CLINICAL DATA INTERCHANGE STANDARDS CONSORTIUM

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Presentation Outline

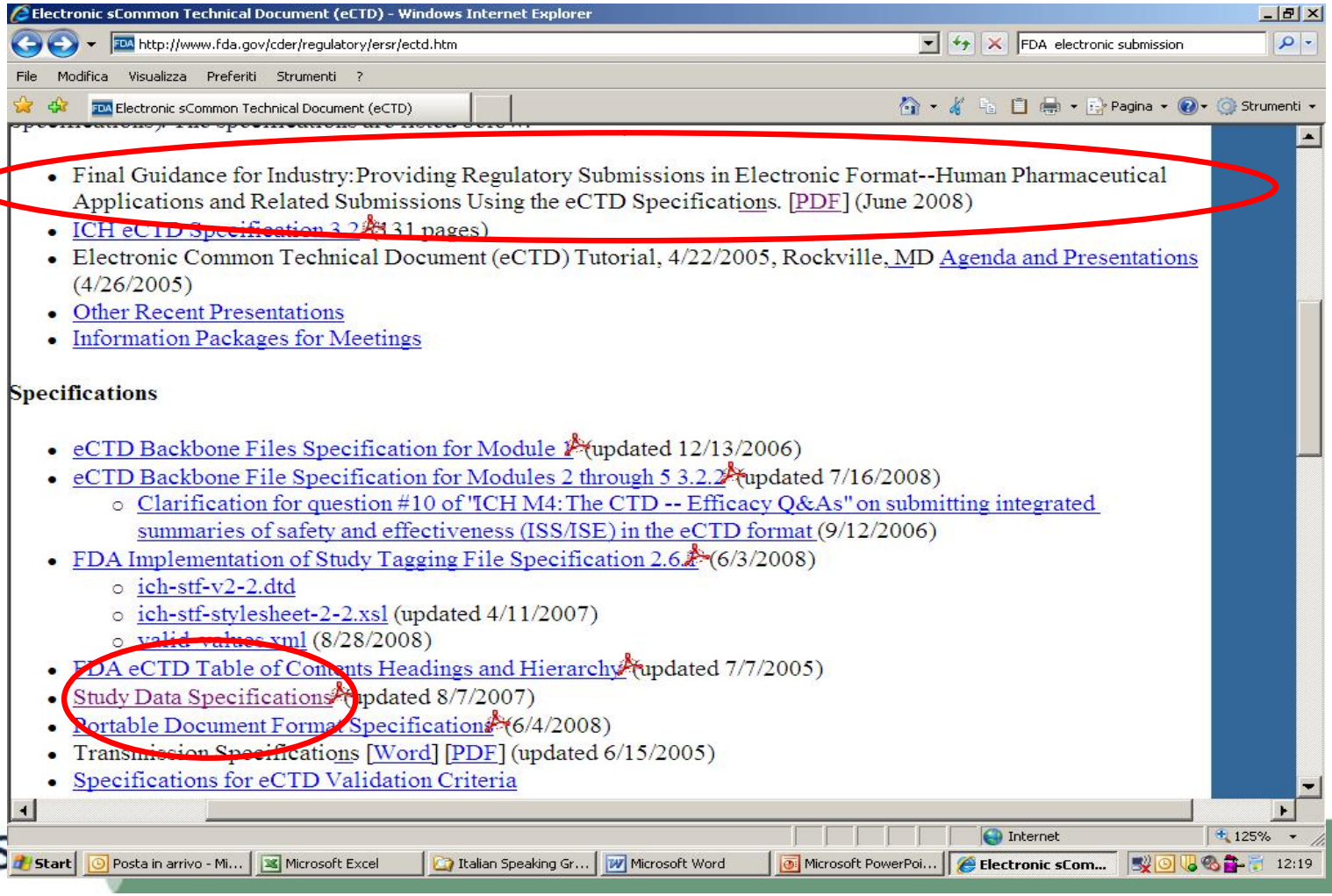
- The FDA requirements
- CDISC Guidelines
  - Overview and general rules
  - Specific rules with examples
- Appearance & format

The FDA reviewer

The FDA requirements

"Study Data Specifications" v.1.4 – 01 Aug 2007 associated to "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format" Revision 2 June 2008*

http://www.fda.gov/cder/regulatory/ersr/ectd.htm



The FDA requirements

Definition

"This is a blank CRF annotations that document the location of the data with the corresponding names of the datasets and the names of those variables included in the submitted datasets."

Specifications

"the annotated CRF is a blank CRF…"

"maps each item on the CRF to the corresponding variables in the database"

"should provide the variable names and coding for each CRF item included in the data tabulation datasets"

"all of the pages and each item in the CRF should be included"

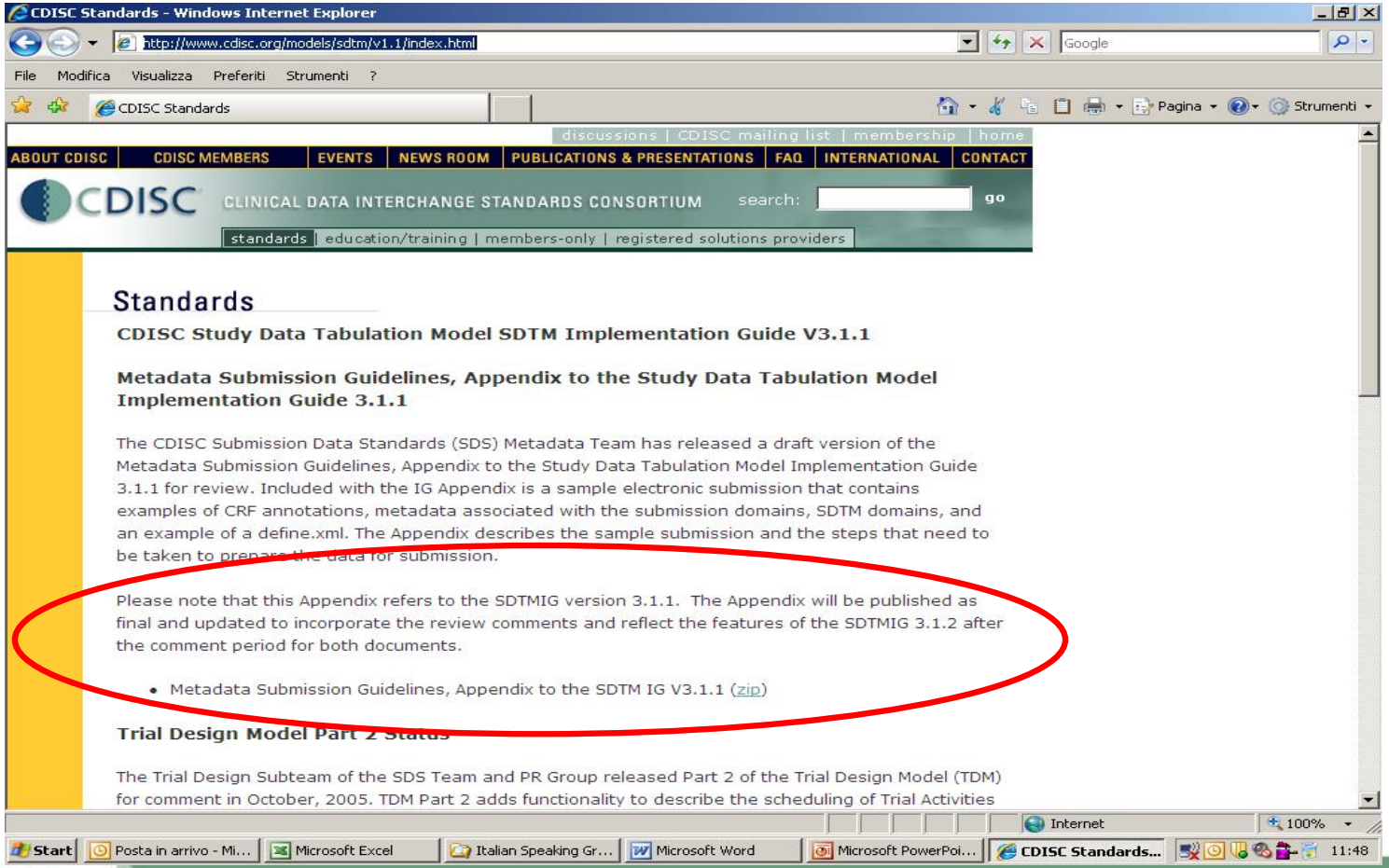
"the sponsor should write *not entered in database* in all items where this applies."

"the annotated CRF should be provided as a PDF file. Name the file *blankcrf.pdf*."

CDISC Guidelines – Overview

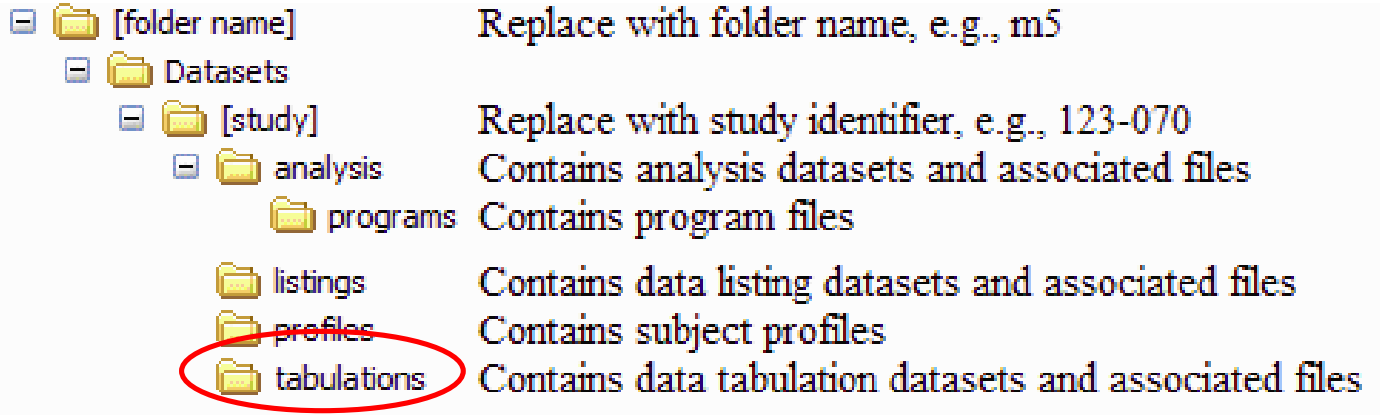
CDISC Metadata Submission Guidelines v. 0.9 (draft for comments – 25 Jul 2007) Appendix to SDTM IG v. 3.1.1

http://www.cdisc.org/models/sdtm/v1.1/index.html



CDISC Guidelines – Overview

- Annotations are meant to **help the FDA reviewer** find the origin of data variables included in the submitted datasets
- Annotated CRF is to be provided to the FDA as a PDF file, named "blankcrf.pdf"
- Sponsors can use their tool to create annotations
- Tool currently used by FDA is Adobe Acrobat Professional
- The "blankcrf.pdf" is stored in the tabulations folder along with the tabulation datasets



CDISC Guidelines – General rules

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- Annotations should reflect the data submitted within the SDTM.
- Annotations of operational or derived data should not be included in the submission.
- Annotations should be text-based and searchable using standard PDF viewers.
- Annotations should not be handwritten on scanned pages.
- Annotations in the “blankcrf.pdf” should appear as simple and as clean as possible.
- Annotations should respect specific appearance and format (color, font) recommendations.

CDISC Guidelines – General rules

- Each unique occurrence of submitted data should be annotated on the CRF.
- Repetitive pages (e.g. Vital signs, Labs) should refer to the original page. A page number or similar reference and link to the associated annotated page should be included (e.g. “For Annotations see CRF page X”).
- Data recorded but not submitted (e.g. Investigator’s signature or questions used for monitoring purposes “Any adverse events?”) should be annotated as “[NOT SUBMITTED]”.
- For some points there is room for interpretation (“may be annotated”, 2-letter prefix and dot before variable name).

Specific rules: one-to-one relationship

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ADVERSE EVENT FORM

Form A **page X/X**

1. Event(s)	2. Pattern of the Event (tick one box only)	3 Seriousness (several statements are possible from 1 to 6)	4. Onset date (dd/mmm/yyyy)	5. End date (dd/mmm/yyyy)	6. Intensity (tick one box only)	7. Action taken (tick one box only)	8. Outcome (tick one box only)	9. Relatedness Is there a reasonable possibility of relatedness? (tick one box only)
AETERM	AEPATT 1. Intermittent 2. Continuous	1. Death 2. Life-threatening 3. Requires hospitalisation or prolonged hospitalisation 4. Disability or Incapacity 5. Congenital anomaly or Birth defect 6. Medically significant 7. None of the above i.e. Not serious	AESTDTC	AEENDTC	AESEV 1. Mild 2. Moderate 3. Severe	AEACN 1. Permanently discontinued 2. Stopped Temporarily 3. Dose reduced 4. Dose increased 5. No action taken 6. Unknown / Not applicable	AEOUT 1. Recovered/Resolved 2. Recovering/Resolving 3. Not recovered/Not resolved 4. Recovered with sequelae/Resolved with sequelae 5. Fatal 6. Unknown	AEREL
	1 2	1 2 3 4 5 6 7 AESDTH			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
	1 2	1 2 3 4 5 6 7 AESLIFE			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
	1 2	1 2 3 4 5 6 7 AESHOSP			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
	1 2	1 2 3 4 5 6 7 AESDISAB			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
	1 2	1 2 3 4 5 6 7 AESCONG			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
	1 2	1 2 3 4 5 6 7 AESMIE			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No
	1 2	1 2 3 4 5 6 7 AESER			1 2 3	1 2 3 4 5 6	1 2 3 4 5 6	Yes No

Specific rules: from horizontal to vertical structure

Vital Signs (VS) Domain:

- Need to annotate fields pre-printed on the CRF (e.g. Systolic Blood Pressure). They become values assumed by a more general variable (VSTESTCD).
- Need for additional description to make the annotation:

  "VSTESTCD when VSTESTCD="SYSBP""

- Topic variable's value (e.g. SYSBP) is used to differentiate the current instance of the annotated variable from the other tests.
- Same applies to VSORRES and VSORRESU.

VS - Common “non-CDISC” annotation

VISIT 1 **VISITNUM**

Not done **q**0 **VSSTAT**

VITAL SIGNS

WEIGHT

Weight |___|___|___| kg

HEIGHT

Height |___|___|___| cm

HR

Heart Rate |___|___|___| beats/min

Blood Pressure |___|___|___| / |___|___|___| mmHg

Systolic **SYSBP** Diastolic **DIABP**

VS Domain SDTMIG 3.1.1.

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6.3.7 Vital Signs — VS

vs.xpt, Vital Signs — Findings, Version 3.1.1, August 26, 2005. One record per vital sign measurement per time point per visit per subject, Tabulatic

Variable Name	Variable Label	Type	Controlled Terms or Format	Origin	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		CRF	Identifier	Unique identifier for a study within the submission.	Req
DOMAIN	Domain Abbreviation	Char	**VS	Derived	Identifier	Two-character abbreviation for the domain most relevant to the observation.	Req
USUBJID	Unique Subject Identifier	Char		Sponsor Defined	Identifier	Unique subject identifier within the submission.	Req
VSSEQ	Sequence Number	Num		CRF or Derived	Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. Can be used to join related records.	Req
VSGRPID	Group ID	Char		Sponsor Defined	Identifier	Used to tie together a block of related records in a single domain to support relationships within the domain and between domains.	Perm
VSSPID	Sponsor-Defined Identifier	Char		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.	Perm
VSTESTCD	Vital Signs Test Short Name	Char	**	CRF or Derived	Topic	Short name of the measurement, test, or examination described in VSTEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in VSTESTCD cannot be longer than 8 characters, nor can it start with a number (e.g.'1TEST'). VSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: SYSBP, DIABP, BMI.	Req
VSTEST	Vital Signs Test Name	Char	**	CRF	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in VSTEST cannot be longer than 40 characters. Examples: Systolic Blood Pressure, Diastolic Blood Pressure, Body Mass Index.	Req
VSCAT	Category for Vital Signs	Char	*	Sponsor Defined	Grouping Qualifier	Used to define a category of related records.	Perm
VSSCAT	Subcategory for Vital Signs	Char	*	Sponsor Defined	Grouping Qualifier	A further categorization of a measurement or examination.	Perm

VS Domain SDTMIG 3.1.1.

Variable Name	Variable Label	Type	Controlled Terms or Format	Origin	Role	CDISC Notes	Core
VSPOS	Vital Signs Position of Subject	Char	*	CRF or Derived	Record Qualifier	Position of the subject during a measurement or examination. Examples: SUPINE, STANDING, SITTING.	Perm
VSORRES	Result or Finding in Original Units	Char		CRF or Derived	Result Qualifier	Result of the vital signs measurement as originally received or collected.	Exp
VSORRESU	Original Units	Char	*	CRF or Derived	Variable Qualifier	Original units in which the data were collected. The unit for VSORRES. Examples: INCHES, FEET, POUNDS, BEATS PER MINUTE.	Exp
VSSTRESC	Character Result/Finding in Std Format	Char		Derived	Result Qualifier	Contains the result value for all findings, copied or derived from VSORRES in a standard format or standard units. VSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in VSSTRESN. For example, if a test has results 'NONE', 'NEG', and 'NEGATIVE' in VSORRES and these results effectively have the same meaning, they could be represented in standard format in VSSTRESC as 'NEGATIVE'. For other examples, see general assumptions.	Exp
VSSTRESN	Numeric Result/Finding in Standard Units	Num		Derived	Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from VSSTRESC. VSSTRESN should store all numeric test results or findings.	Exp
VSSTRESU	Standard Units	Char	*	CRF or Derived	Variable Qualifier	Standardized unit used for VSSTRESC or VSSTRESN.	Exp
VSNRIND	Reference Range Indicator	Char	*	CRF or Derived	Variable Qualifier	1. Indicates where value falls with respect to reference range (which could be defined by VSORNRLO and VSORNRHI or by VSSTNRC (if those variables are used). Examples: NORMAL, ABNORMAL, HIGH, LOW. 2. Should not be used to indicate clinical significance.	Perm
VSSTAT	Vitals Status	Char	**NOT DONE	CRF or Derived	Record Qualifier	Used to indicate that a vital sign measurement was not done. Should be null if a result exists in VSORRES.	Perm
VSREASND	Reason Not Performed	Char		CRF or Derived	Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with VSSTAT when value is NOT DONE.	Perm
VSLOINC	LOINC Code	Char	**	Derived	Synonym Qualifier	1. LOINC Code for VSTEST. 2. The LOINC version should be provided in the Sponsor Comments column in the data definition document.	Perm
VSLOC	Location of Vital Signs Measurement	Char	*	CRF or Derived	Record Qualifier	Location relevant to the collection of Vital Signs measurement. Example: LEFT ARM for blood pressure.	Perm

From non-CDISC to CDISC

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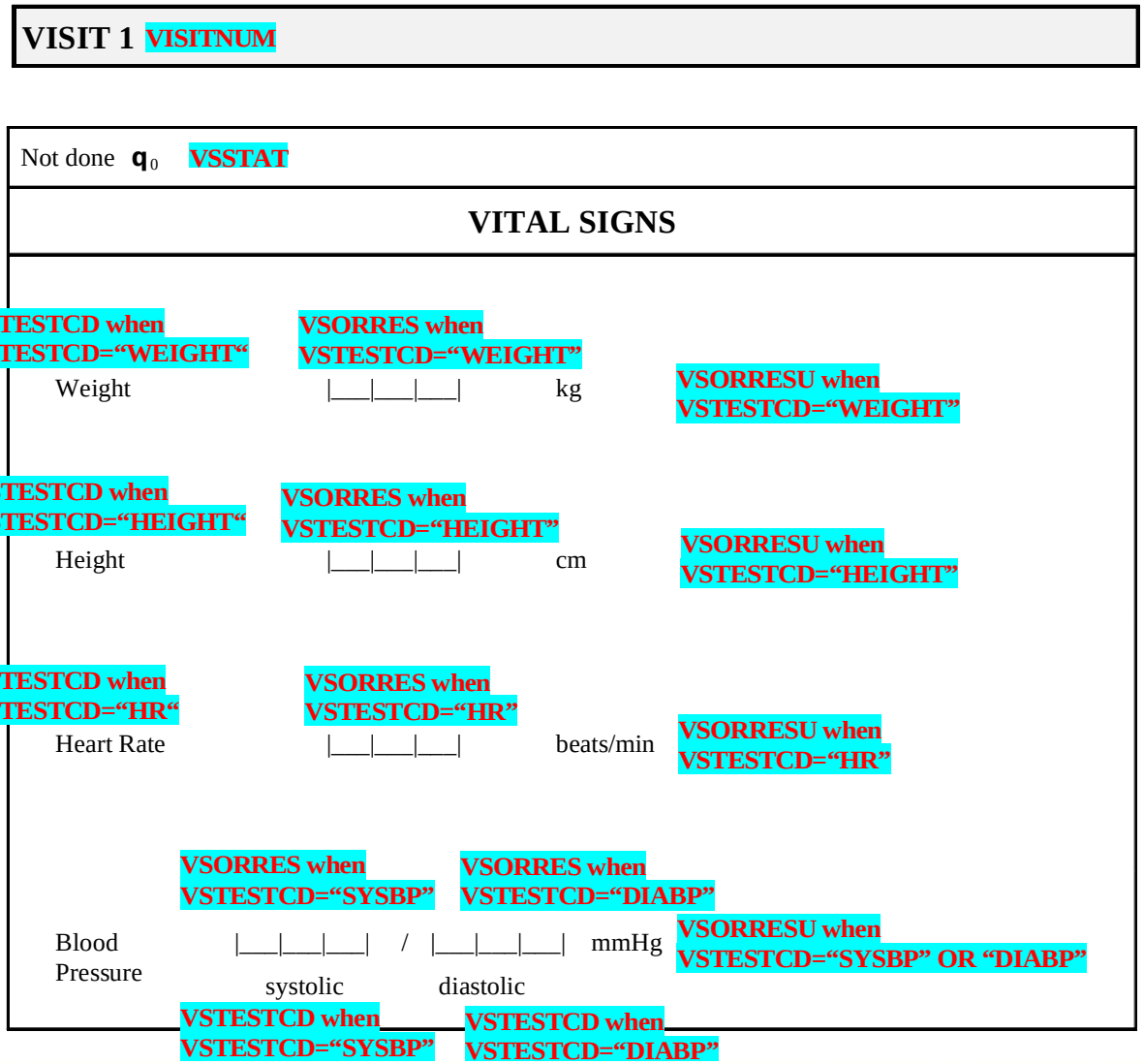
PATIENT	WEIGHT (kg)	HEIGHT (cm)	HR (bmp)	DBP (mmHg)	SBP (mmHg)
001	85	180	70	80	120

USUBJID	VSTESTCD	VSTEST	VSORRES	VSORRESU
CH-001	WEIGHT	Weight	85	kg
CH-001	HEIGHT	Height	180	cm
CH-001	HR	Heart Rate	70	bpm
CH-001	DIABP	Diastolic Blood Pressure	80	mmHg
CH-001	SYSBP	Systolic Blood Pressure	120	mmHg

VS - CDISC annotation



Annotating each variable data from different CRF pages

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Disposition (DS) Domain:

- provides an accounting for all subjects who entered the study.
- may include protocol milestones (protocol-specified event), such as informed consent and randomization, as well as the subject's completion status or reason for discontinuation.

DS Domain SDTMIG 3.1.1.

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6.2.2 Disposition — DS

ds.xpt, Disposition — Events Version 3.1.1, August 26, 2005. One record per disposition status or protocol milestone per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms or Format	Origin	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		CRF	Identifier	Unique identifier for a study within the submission.	Req
DOMAIN	Domain Abbreviation	Char	**DS	Derived	Identifier	Two-character abbreviation for the domain most relevant to the observation.	Req
USUBJID	Unique Subject Identifier	Char		Sponsor Defined	Identifier	Unique subject identifier within the submission.	Req
DSSEQ	Sequence Number	Num		CRF or Derived	Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. Can be used to join related records.	Req
DSGRPID	Group ID	Char		Sponsor Defined	Identifier	Used to tie together a block of related records in a single domain to support relationships within the domain and between domains.	Perm
DSREFID	Reference ID	Char		Sponsor Defined	Identifier	Optional internal or external identifier.	Perm
DSSPID	Sponsor-Defined Identifier	Char		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.	Perm
DSTERM	Reported Term for the Disposition Event	Char		CRF	Topic	Verbatim name of the event or protocol milestone. Some terms in DSTERM will match DSDECOD, but others, such as 'Subject moved,' will map to controlled terminology in DSDECOD, such as 'LOST TO FOLLOW-UP.'	Req

DS Domain SDTMIG 3.1.1.

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Variable Name	Variable Label	Type	Controlled Terms or Format	Origin	Role	CDISC Notes	Core
DSDECOD	Standardized Disposition Term	Char	*	CRF or Derived	Synonym Qualifier	Controlled terminology for the name of disposition event or protocol milestone. Examples of disposition events: COMPLETED, ADVERSE EVENT, DEATH, LACK OF EFFICACY, LOST TO FOLLOW-UP, NON-COMPLIANCE WITH STUDY DRUG, PHYSICIAN DECISION, PREGNANCY, PROGRESSIVE DISEASE, PROTOCOL VIOLATION, SCREEN FAILURE, STUDY TERMINATED BY SPONSOR, TECHNICAL PROBLEMS, WITHDRAWAL OF CONSENT, OTHER. Examples of protocol milestones: INFORMED CONSENT OBTAINED, RANDOMIZED	Req
DSCAT	Category for Disposition Event	Char	*	Sponsor Defined	Grouping Qualifier	Used to define a category of related records. Examples: DISPOSITION EVENT or PROTOCOL MILESTONE.	Perm
DSSCAT	Subcategory for Disposition Event	Char	*	Sponsor Defined	Grouping Qualifier	A further categorization of disposition event.	Perm
VISIT	Visit Name	Char		CRF or Derived	Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm
VISITNUM	Visit Number	Num		CRF or Derived	Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Perm
VISITDY	Planned Study Day of Visit	Num		CRF or Derived	Timing		Perm
EPOCH	Trial Epoch	Char	*	CRF or Derived	Timing	EPOCH may be used when DSCAT = 'DISPOSITION EVENT'. Examples: TREATMENT PHASE, SCREENING, FOLLOW-UP	Perm
DSDTC	Date/Time of Collection	Char	ISO 8601	CRF or Derived	Timing		Perm
DSSTDTC	Start Date/Time of Disposition Event	Char	ISO 8601	CRF or Derived	Timing		Exp
DSSTDY	Study Day of Start of Disposition Event	Num		Derived	Timing	Study day of start of the disposition event relative to the sponsor-defined RFSTDTC.	Perm

** indicates variable may be subject to sponsor-controlled terminology; ** indicates variable may be subject to external controlled terminolo*

DS Domain - Example

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USUBJID	DSTERM	DSDECOD	DSCAT	VISITNUM	DSDTC	DSSTDTC
CH-001	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	PROTOCOL MILESTONE	1	2009-01-12	2009-01-12
CH-001	RANDOMIZED	RANDOMIZED	PROTOCOL MILESTONE	2	2009-01-26	2009-01-26
CH-001	SUBJECT MOVED	LOST TO FOLLOW-UP	DISPOSITION EVENT	3	2009-03-06	2009-03-06

DS - CDISC annotation

VISIT VISITNUM	Visit Date: |___|___| |___|___|___| |___|___| D D M M M Y Y

DSTERM when DSTERM="INFORMED CONSENT OBTAINED"

INFORMED CONSENT

Participation agreement attestation:

I the undersigned, ……., certify that the patient's written informed consent form has been [NOT SUBMITTED] read, understood, approved and signed by the patient after having received information.

DSSTDTC when DSTERM=" INFORMED CONSENT OBTAINED"

Date of written informed consent signature |___|___| |___|___|___| |___|___|___|___|
D D M M M Y Y Y Y

Investigator's Signature: ..……..

[NOT SUBMITTED]

DS - CDISC annotation

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VISIT 2 **VISITNUM**

DSTERM when DSTERM= "RANDOMIZED"

RANDOMISATION

Can the patient be randomised?	Yes **q** No **q**

If "Yes", please enter:

Randomisation Date: |__|__| |__|__|__| |__|__|__|__|
D D M M M Y Y Y Y

DSSTDTC when DSTERM="RANDOMISED"

Randomisation no. |___|___|___|

Please attach the label of the study medication here

If "No", please fill in the Study Termination Form.

STUDY TERMINATION

Indicate the subject status at the time of completion/discontinuation.

In case of discontinuation the Primary Reason should be ticked

DSTERM="COMPLETED" when DSCAT= "DISPOSITION EVENT" Completed	q 0	
DSTERM="ADVERSE EVENT" when DSCAT= "DISPOSITION EVENT" Discontinued due to adverse event	q 1	Please fill in Adverse Event Form
DSTERM Discontinued due to lack of efficacy	q 2	
DSDECOD="LOST TO FOLLOW-UP" when DSCAT= "DISPOSITION EVENT" Discontinued due to lost to follow-up	q 3	Please specify ……**DSTERM**.....
DSTERM Discontinued due to recovery	q 4	
DSTERM Development of study specific discontinuation criteria	q 5	
Discontinued due to non compliance with **DSTERM** study drug	q 6	
DSTERM Discontinued due to Death	q 7	Please fill in the both the Adverse Event and Serious Adverse Event Forms
DSTERM Discontinued due to withdrawal of consent	q 8	
DSDECOD Other	q 9	Please specify ……**DSTERM**.....

Date of completion/discontinuation |___|___| |___|___|___| |___|___|___|___|
D D M M M Y Y Y Y

DSSTDTC when DSCAT= "DISPOSITION EVENT"

Wildcard characters for domains

Some data collection fields relate to variables in more than one domain.

E.g. dates recorded in the page header at the beginning of the visit.

These fields should be annotated as:

“ - - DTC” where “ - - ” generically represents the 2-letter domain prefix (DS, DM, MH, etc.) and “DTC” is the shared variable designator.

The comment string should continued with a comma-delimited string of specific variables enclosed in square brackets “ -- DTC [DSDTC, DMDTC, MHDTC]”.

Chiesi Farmaceutici S.p.A **Clinical Study No. STUDYID**

Centre No. |___|___|___| |___|___|___| **Screening No.** |___|___|___|
SITEID **SUBJID**

VISIT 1 VISITNUM Visit Date: |___|___| |___|___|___| |___|___|
D D M M M Y Y

- - DTC [DSDTC, DMDTC, MHDTC] when VISITNUM = "1"

INFORMED CONSENT

Participation agreement attestation:

I the undersigned, ……., certify that the patient's written informed consent form has been read, understood, approved and signed by the patient after having received information.

Date of written informed consent signature |___|___| |___|___|___| |___|___|___|___|
D D M M M Y Y Y Y

Investigator's Signature: ..……..

DEMOGRAPHY

Date of Birth |___|___| |___|___|___| |___|___|___|___|
D D M M M Y Y Y Y

Sex Male **q**

Female **q**

Supplemental Qualifier variables

SDTM does not allow the addition of new variables.

Non-standard variables and values are captured in the Supplemental Qualifier (SUPPQUAL) datasets together with the parent domain (domain the supplemental qualifiers relates back to).

Supplemental qualifier variables should be annotated using a 2-part name separated by a dot:

1st part: “SUPP - -” where “- -” denotes the 2-letter parent domain

2nd part: exact value of QNAM

e.g. SUPPDM.QVAL when QNAM=”RAND”

SUPPQUAL - Example

parent domain

short name of the qualifier variable

value assumed by QNAM

USUBJID	RDOMAIN	QNAM	QLABEL	QVAL
CH-001	DM	RAND	Randomized	Y
CH-001	DM	RANDNO	Randomization no.	23

SUPPQUAL - CDISC annotation

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VISIT 2

RANDOMISATION

Can the patient be randomised?	Yes q No q **SUPPDM.QVAL when QNAM="RAND"**

If "Yes", please enter:

Randomisation Date: |__|__| |__|__|__| |__|__|__|__|
D D M M M Y Y Y Y

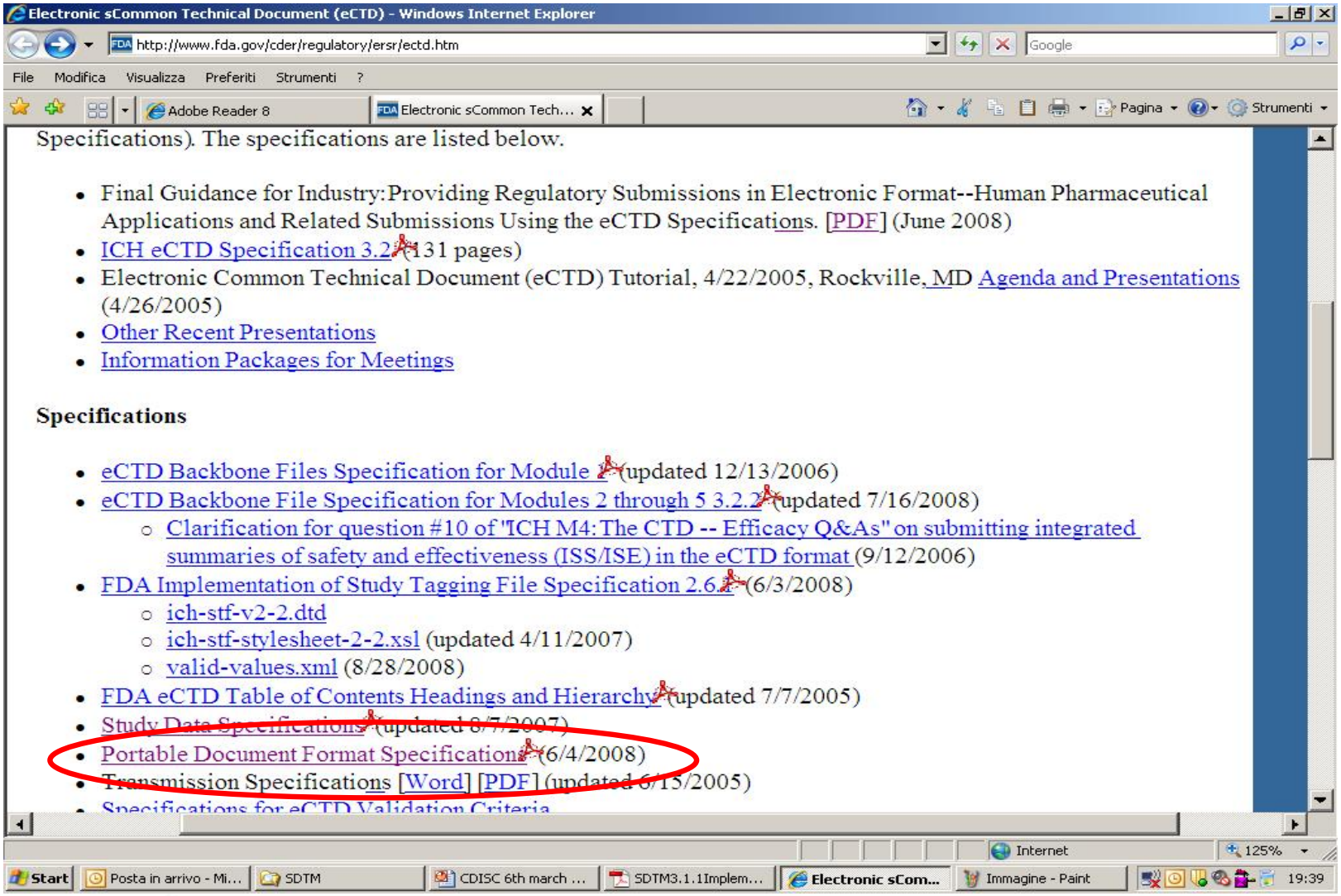
Randomisation no. |___|___|___| **SUPPDM.QVAL when QNAM="RANDNO"**

Please attach the label of the study medication here

If "No", please fill in the Study Termination Form.

The FDA requirements – appearance & format

"Portable Document Format Specifications" v 2.0 – 06 Jun 2008



The FDA requirements – appearance & format

Applicable to all .pdf documets (no CRF annotated specific)

Very detailed requirements in terms of:

- Font
- Font size
- Page orientation
- Page size and margins
- Source of electronic document
- Bookmarks and hyperlinks

Aims: to facilitate reviewer (search, navigate) and to avoid problems which can affect the document appearance, structure and content.

CDISC Guidelines – appearance & format

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Reflects FDA general requirements for .pdf documents but is specific for annotated CRF:

- All text which represent variable names CAPITALIZED.
- **Font color**: color not used for text on the page.
- Fill-in color: contrasting color for the comment.
- Recommended annotation: “free text” annotation.
- Font: comments in **Arial Bold Italic** font.
- Text size: equivalent in size to 12-point Times Roman, if possible.
- Bookmarks: for each visit and each form.

Questions?

Thank you!

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Marco Costantini

Giada Rizzi

Chiesi Farmaceutici S.p.A.

Corporate Biometrics & Data Management

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