
The Good? the Bad? or the Ugly?
CDISC eSubmission packages in practice



What does CDISC eSubmission package consists of?

SDTM

define.xml (+stylesheet)

CSDRG

aCRF

complexalgorithms

ADAM

define.xml (+stylesheet)

ADRG

programs

programtoc

Annotated crf

aCRF – and how to get it wrong



DOMAIN: DM

FORM:DEM

MIGR_R3.0_007_14NOV2016_AB: Master Form

Project Name: BN29739

Form: Demographics

Generated On: 16 Dec 2016 14:54:11

For reference purpose
ONLY. This CRF should
not be used by the
clinical investigative site
as source documentation

Field Name	SAS Label	Values	
1 BRTHD	Date of Birth		DM.BRTHDTC (Date part)
2 AGEIC	Age		DM.AGE
3 AGEU	Age Unit	YEARS	DM.AGEU
4 SEX	Sex	MALE = Male FEMALE = Female	DM.SEX
5 ETHNIC	Ethnicity	HISPANIC OR LATINO = Hispanic or Latino NOT HISPANIC OR LATINO = Not Hispanic or Latino NOT REPORTED = Not reported UNKNOWN = Unknown	DM.ETHNIC

DM.RACE, if only one value is selected. DM.RACE = 'MULTIPLE',
if more than one value is selected.
RACEN in SUPPDM where n = 1 to N selected values

7 INDALK	American Indian or Alaska Native	DM.RACE1
8 ASIAN	Asian	DM.RACE2
9 BLACK	Black or African American	DM.RACE3

aCRF – and how to do it better

DM = Demographics

SUPPDM = Supplemental Qualifiers for DM

MIGR_R12.0_ESC_013_04DEC19_RDA: Master

Project Name: WO29522

Form: Demographics

Generated On: 21 May 2020 06:58:03

Day month and year of birth		DM.BRTHDTC	
Age	DM.AGE		
Age unit		DM.AGEU	YEARS
Sex		DM.SEX	Male ☐
			Female ☐
Ethnicity			Hispanic or Latino ☐
		DM.ETHNIC	Not Hispanic or Latino ☐
			Not reported ☐
			Unknown ☐
Race (select all that apply):		DM.RACE	
American Indian or Alaska Native		RACE1 in SUPPDM	
Asian		RACE2 in SUPPDM	
Black or African American		RACE3 in SUPPDM	
Native Hawaiian or Other Pacific Islander		RACE4 in SUPPDM	
White		RACE5 in SUPPDM	
If race is Asian, specify region			Indian subcontinent ☐
		RACESCAT in SUPPDM	Other than Indian subcontinent ☐
Form source	[NOT SUBMITTED]		DEM

DOMAIN: DM
FORM: DEM

MIGR_R3.0_007_14NOV2016_AB: Master Form

Project Name: BN29739

Form: Demographics

Generated On: 16 Dec 2016 14:54:11

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Project Name: WO29522

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Generated On: 21 May 2020 06:58:03

Day month and year of birth

Age

Age unit YEARS

Sex Male ☐
Female ☐

Ethnicity Hispanic or Latino ☐
Not Hispanic or Latino ☐
Not reported ☐
Unknown ☐

Race (select all that apply):

American Indian or Alaska Native

Asian

Black or African American

Native Hawaiian or Other Pacific Islander

White

If race is Asian, specify region Indian subcontinent ☐
Other than Indian subcontinent ☐

Form source DEM

define.xml

CDISC01_1

[Annotated CRF](#)[► Supplemental Documents](#)[Standards](#)[► Datasets](#)[► Controlled Terminology](#)[► Methods](#)[Expand all VLM](#)[Collapse all VLM](#)

Date/Time of Define-XML document generation: 2019-02-11T15:30:01

Define-XML version: 2.1.0

Define-XML Context: Other

Stylesheet version: 2019-02-11

Study Name CDISC01_1**Study Description** CDISC Test Study Modified to illustrate Define-XML 2.1 features**Protocol Name** CDISC01-1**Metadata Name** Study CDISC01_1, Data Definitions V-1**Metadata Description** Data Definitions for CDISC01-01 SDTM datasets. This metadata version contains only a subset of datasets compared to the prior version. The metadata provided is only intended to illustrate most Define-XML 2.1 new features and not meant to serve as a comprehensive example of all metadata expected to be defined to fully describe an SDTM dataset package. Notes: 1) Supplemental documents released in prior Define-XML versions were not updated to reflect changes to the metadata. 2) This example is prepared for a context other than submission; however, still using the approach of non-standard variables prepared as supplemental qualifiers datasets.

Standards for Study CDISC01_1

Standard	Type	Status	Documentation
SDTMIG 3.1.2	IG	Final	The CDISC01 study was modeled on a very old SDTMIG and no attempt was done yet to upversion it to a newer SDTMIG
SDTMIG 3.2	IG	Final	As an example, the CDISC01 study was adjusted to include a new Domain available in SDTM IG 3.2
SDTMIG-MD 1.0	IG	Final	As an example, the CDISC01 study was adjusted to include a new Domain available in SDTMIG-MD 1.0. The XS Domain is expected to reference the device used with variable SPDEVID.
CDISC/NCI SDTM 2011-12-09	CT	Final	Assuming the CT was not upversioned for this study
CDISC/NCI SDTM 2015-12-18	CT	Final	The CT version applicable for the new Domain is the 2015-12-18 version

Datasets

Dataset	Description	Class	Structure	Purpose	Keys	Documentation	Location
TS [SDTMIG 3.1.2]	Trial Summary	TRIAL DESIGN	One record per trial summary parameter value	Tabulation	STUDYID, TSPARMCD, TSSEQ		ts.xpt
DI [SDTMIG-MD 1.0]	Device Identifiers	SPECIAL PURPOSE	One record per device identifier per device	Tabulation	STUDYID, SPDEVID, DIPARMCD	The DI domain is included to illustrate the use of a separate complementary SDTMIG. In this example, the device ID is referenced from a Findings Domain (XS).	di.xpt
DM [SDTMIG 3.1.2]	Demographics	SPECIAL PURPOSE	One record per subject	Tabulation	STUDYID, USUBJID	See Reviewer's Guide, Section 2.1 Demographics Reviewers Guide [section2.1]	dm.xpt
EC [SDTMIG 3.2]	Exposure as Collected	INTERVENTIONS	One record per constant dosing interval per subject	Tabulation	STUDYID, USUBJID, ECSTDTC, ECENDTC, ECTRT, ECDOSE		ec.xpt
EX [SDTMIG 3.1.2]	Exposure	INTERVENTIONS	One record per constant dosing interval per subject	Tabulation	STUDYID, USUBJID, EXSTDTC, EXENDTC, EXTRT, EXDOSE		ex.xpt

Example variable metadata - define.xml

LBTESTCD		Lab Test or Examination Short Name	text	7	Laboratory Test Code [10 Terms]	Assigned (Source: Sponsor)
LBTEST		Lab Test or Examination Name	text	22	Laboratory Test Name [10 Terms]	Collected (Source: Vendor)
LBCAT		Category for Lab Test	text	10		Collected (Source: Vendor)
LBORRES VLM		Result or Finding in Original Units	text	8		Origin specified at Value Level Metadata
	LBTESTCD IN ("BILI" (Bilirubin), "GLUC" (Glucose)) and LBSPEC = "BLOOD"	Result or Finding in Orig Units - Set 1	float	3		Collected (Source: Vendor) From Central lab (LB.LBNAM NE "LOCAL LAB")
	LBTESTCD IN ("BUN" (Blood Urea Nitrogen), "HGB" (Hemoglobin), "LYM" (Lymphocytes)) and LBSPEC = "BLOOD"	Result or Finding in Orig Units - Set 2	float	4		Collected (Source: Vendor) From Central lab (LB.LBNAM NE "LOCAL LAB")
	LBTESTCD IN ("GLUC" (Glucose), "OCCBLD" (Occult Blood)) and LBSPEC = "URINE"	Result or Finding in Orig Units Set 3	text	8		Collected (Source: Vendor) From Central lab (LB.LBNAM NE "LOCAL LAB")
	LBTESTCD = "HCT" (Hematocrit) and LBSPEC = "BLOOD" and LBNAM ≠ "LOCAL LAB"	Hematocrit	float	4		Collected (Source: Vendor) From Central lab (LB.LBNAM NE "LOCAL LAB")

Example variable metadata - define.pdf

Variable Name	Label	Type	Formats (Codes)	Origin	Comments
LBSPID	Sponsor-Defined Identifier	char		LB.LBSPID	Set to Sponsor-Defined Identifier to the appropriate Clinical Data Management System or dataset identifiers. Data was also received electronically
LBTESTCD	Lab Test or Examination Short Name	char		DERIVED	Set to the Lab Test Short Name based on the reported test code. Data was also received electronically
LBTEST	Lab Test or Examination Name	char		DERIVED	Set to the Test Name associated with the Test Short Name LB.LBTESTCD
LBCAT	Category for Lab Test	char		DERIVED	Values: 'CHEMISTRY','HEMATOLOGY','IMMUNOLOGY','SEROLOGY','URINALYSIS','VIR OLOGY'. Set to the associated category with the Lab Test Short Name. Data was also received electronically
LBORRES	Result or Finding in Original Units	char		LB.LBORRES	Data was also received electronically

Codelists

Vital Signs (VS) [Location: [vs.xpt](#)]

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin
STUDYID	Study Identifier	1	text	7		Protocol
DOMAIN	Domain Abbreviation		text	2		Assigned
USUBJID	Unique Subject Identifier	2	text	19		Derived
VSSEQ	Sequence Number		integer	3		Derived
VSGRPID	Group ID		text	13		Assigned
VSSPID	Sponsor-Defined Identifier		text	10		Assigned
VSTESTCD	Vital Signs Test Short Name	3	text	6	Vital Signs Test Code	CRF Pages 20 21 23
VSTEST	Vital Signs Test Name		text	24	Vital Signs Test Name	Assigned

Codelists...

In SDTM

Vital Signs Test Code [C66741]

Permitted Value (Code)	Display Value (Decode)
DIABP [C25299]	Diastolic Blood Pressure
HEIGHT [C25347]	Height
PULSE [C49676]	Pulse Rate
RESP [C49678]	Respiratory Rate
SYSBP [C25298]	Systolic Blood Pressure
TEMP [C25206]	Temperature
VSALL [*]	Vital Signs
WEIGHT [C25208]	Weight

* Extended Value

... that are not matching ADAM

Vital Signs Test Code [C66741]

Permitted Value (Code)
ABRIDX [N87304]
TBRIDX [*]
VBFATM [*]
VSALL [*]
CIRCUMF [*]
PALPBLTY [*]
BFATTBMP [*]
PULSEPR [C100945]
FARMCIR [C100946]
HIPCIR [C100947]
WSTCIR [C100948]

What is the truth?

Were any vital signs collected at this visit?		VS.VSSTAT when VSTESTCD ='VSALL'	Yes ☐
			No ☐
Weight	VS.VSORRES when VSTESTCD ='WEIGHT'	Fixed Unit: kg	
Weight unit	VS.VSORRESU when VSTESTCD ='WEIGHT'	KG	
Form source	[NOT SUBMITTED]	VTLS4	
Planned timepoint	VS.VSTPT	60 MIN BEFORE INFUSION ☐	
		DURING INFUSION ☐	
		AFTER INFUSION ☐	
		TREATMENT ☐	
		DISCONTINUATION ☐	
Not done	[NOT SUBMITTED]	☐	
Vital signs date	VS.VSDTC		
Vital signs time	VS.VSDTC		
Vital signs time unknown	[NOT SUBMITTED]	☐	
Temperature	VS.VSORRES when VSTESTCD ='TEMP'	Fixed Unit: C	
Temperature unit	VS.VSORRESU when VSTESTCD ='TEMP'	C	
Pulse	VS.VSORRES when VSTESTCD ='PULSE'	Fixed Unit: beats/min	
Pulse unit	VS.VSORRESU when VSTESTCD ='PULSE'	BEATS/MIN	
Respiratory rate	VS.VSORRES when VSTESTCD ='RESP'	Fixed Unit: breaths/min	
Respiratory rate unit	VS.VSORRESU when VSTESTCD ='RESP'	BREATHS/MIN	
Systolic blood pressure	VS.VSORRES when VSTESTCD ='SYSBP'	Fixed Unit: mmHg	
Diastolic blood pressure	VS.VSORRES when VSTESTCD ='DIABP'	Fixed Unit: mmHg	
Blood pressure measurement unit	VS.VSORRESU when VSTESTCD ='DIABP' or 'SYSBP'	MMHG	

More examples

One data model vs another

Epoch [C99079]

Permitted Value (Code)
FOLLOW-UP [C99158]
SCREENING [C48262]
TREATMENT [C101526]

Epoch [C99079]

Permitted Value (Code)
NOT APPLICABLE [C48660]
TREATMENT [C101526]
BLINDED TREATMENT [C102255]
OPEN LABEL TREATMENT [C102256]
CONTINUATION TREATMENT [C123452]
INDUCTION TREATMENT [C123453]
BASELINE [C125938]
LONG-TERM FOLLOW-UP [C16032]
WASHOUT [C42872]
SCREENING [C48262]
RUN-IN [C98779]
FOLLOW-UP [C99158]

More examples

One data model vs another

Dose Units in Exposure [C71620]

Permitted Value (Code)
mg [C28253]
mg/m2 [C67402]

Unit [C71620]

Permitted Value (Code)
ug/L/h [C122229]
mg/m [*]
g/m [*]
mol/L [C48555]
10 ³ /L [C105519]
10 ⁶ /L [C67452]
K/mm [*]
106/mm [*]
106/L [*]
millions/L [*]
TITER UNITS [*]
U/ml [*]
M/l [*]
M/mm [*]
UI/ml [*]

Study data reviewer's guide

Inconsistencies

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM v1.2 & 1.3/SDTM Implementation Guide 3.1.2 & 3.1.3
ADaM	Analysis Data Model Document v2.1 ADaM Implementation Guide v1.0
Controlled Terminology	CDISC SDTM Terminology 2015-06-26 CDISC ADaM Terminology 2016-06-24
Data Definitions	Define.xml v2.0
Medical Events Dictionary	MedDRA v18.0

1.4 Source Data Used for Analysis Dataset Creation

The source data for the ADaM datasets are SDTM versions 1.2 & 1.3.

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: GX29503

Protocol Title: A Phase 1, Open-Label, Single-Arm Study in Healthy Subjects to Evaluate Pain, Tolerability, Safety, and Usability of a Prefilled Autoinjector to Self-Administer Etrolizumab Subcutaneously

Protocol Versions: Final – 21 July 2015

2.2 Protocol Design in Relation to ADaM Concepts

1.2 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	Client SDTMv Specification 21Sep2015, based on SDTM v1.3/SDTM IG 3.1.2 Amendment 1
Controlled Terminology	2015-06-26
Data Definitions	Define.xml v2.0
Medications Dictionary	WHO Drug Version March 2015 Enhanced Dictionary Version B2 format
Medical Events Dictionary	MedDRA Version 18.0

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: GX29503

Protocol Title: A Phase 1, Open-Label, Single-Arm Study in Healthy Subjects to Evaluate Pain, Tolerability, Safety, and Usability of a Prefilled Autoinjector to Self-Administer Etrolizumab Subcutaneously

Protocol Versions: 1.0 - 21 July 2015
2.0 - 13 November 2015

2.2 Protocol Design

Conformance summary - a horror

4.2 Issues Summary

Dataset	Diagnostic Message	Severity	Count	Explanation
AE	Value for AEBODSYS not found in (SOC) CT codelist	Warning	29	Codelist is Extensible
AE	Variable appears in dataset, but is not in SDTM standard	Warning	15	Per client specification
AE	SDTM/dataset variable label mismatch	Warning	1	Per client specification
AE	Non-recommended variable length	Warning	7	Per client specification
CE	Variable appears in dataset, but is not in SDTM standard	Warning	1	Per client specification
CE	Non-recommended variable length	Warning	2	Per client specification
CM	Value for CMDOSFRQ not found in (FREQ) CT codelist	Warning	5	Codelist is Extensible

Conformance summary - a horror continues...

Dataset	Diagnostic Message	Severity	Count	Explanation
TA	SDTM/dataset variable label mismatch	Warning	1	Per client specification
TS	NULL value in variable marked as Required	Error	4	Per client specification
TS	Value for TSVAL not found in (TPHASE) CT codelist	Warning	1	Codelist is Extensible
TS	Value for TSPARM not found in (TSPARM) CT codelist	Warning	4	Codelist is Extensible
TS	Value for TSPARMCD not found in (TSPARMCD) CT codelist	Warning	2	Codelist is Extensible
TS	Variable appears in dataset, but is not in SDTM standard	Warning	4	Per client specification
TS	SDTM/dataset variable label mismatch	Warning	1	Per client specification
VS	Value for VSORRESU not found in (VSRESU) CT codelist	Warning	158	Codelist is Extensible
VS	Value for VSSTRESU not found in (VSRESU) CT codelist	Warning	158	Codelist is Extensible
VS	Invalid VISIT/VISITNUM	Warning	6	Unscheduled VISIT/VISITNUM do not appear in the TV dataset
VS	Non-recommended variable length	Warning	1	Per client specification
XP	Non-recommended variable length	Warning	2	Per client specification
ZA	Invalid VISIT/VISITNUM	Warning	3	Unscheduled VISIT/VISITNUM do not appear in the TV dataset
ZA	Non-recommended variable length	Warning	1	Per client specification

Conformance summary - what should it be then?

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
DD0024	Invalid Term in codelist 'Action Taken with Study Treatment' for variable 'AEACN'	Warning	DEFINE	1 (100.00%)	MULTIPLE is a CDISC general terminology concept used to indicate more than one response given. Individual action taken responses are found in SUPPAE.QVAL when QNAM in AEACN1 - AEACN8.

Conformance summary - what should it be then?

Check ID	Diagnostic Message	FDA Severity	Dataset	Count (Issue Rate)	Explanation
SD0024	Missing value for FADTC, when FAENDTC is provided	Warning	FA	4 (< 0.1%)	Data issue. FADTC (mapped from Visit Date) is missing for these records, whereas FADTDC and FAENDTC (mapped from Date Administered) are present with Start/End Times.

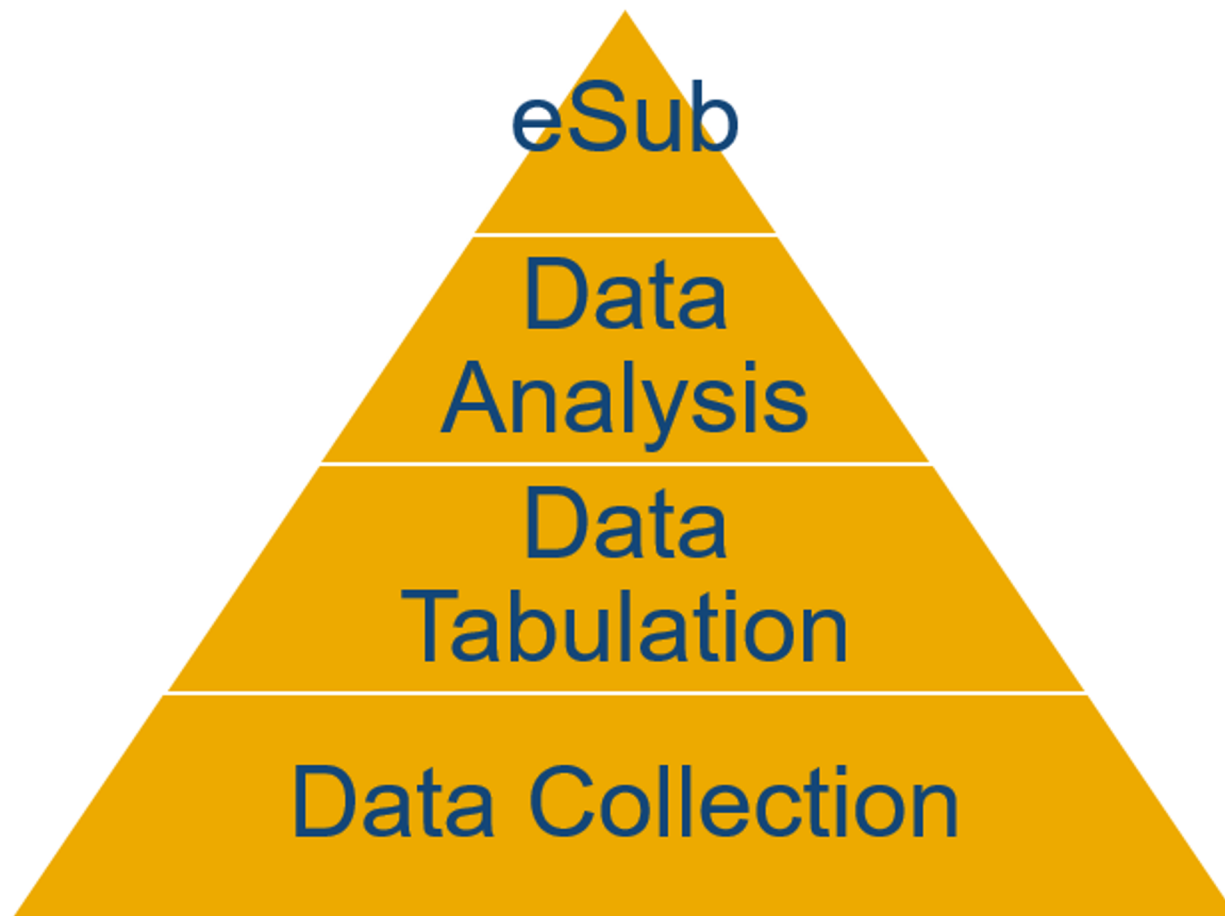
Ways of doing Incl/Excl criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
2	EXCLUSION	EXCL11	Receipt of any of the following: Emicizumab in a prior investigational study An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration A non-hemophilia-related investigational drug within last 30 days or 5 half-lives, whichever is shorter Any other investigational drug currently being administered or planned to be administered
2	EXCLUSION	EXCL12	Inability to comply with the study protocol in the opinion of the investigator
2	EXCLUSION	EXCL13	Pregnancy or lactation or intention to become pregnant during the study
2	EXCLUSION	EXCL14	Women with a positive serum pregnancy test result within 7 days prior to initiation of study drug
2	EXCLUSION	EXCL15	Patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgment
3	INCLUSION	INCL01	Signed Informed Consent Form (consent/assent will be taken as appropriate)
3	INCLUSION	INCL02	Aged ≥ 12 years
3	INCLUSION	INCL03	Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the patient-reported outcome (PRO) questionnaires and bleed diaries through the use of an electronic device
3	INCLUSION	INCL04	Body weight ≥ 40 kg at screening
3	INCLUSION	INCL05	Diagnosis of severe congenital hemophilia A or hemophilia A with FVIII inhibitors

Ways of doing Incl/Excl criteria

Protocol/ Amendment Version	Category	IETESTCD	Full Text of Criterion
Versions- 1,2,3,4,5	INCLUSION	INCL01	Have documented previously untreated CLL according to IWCLL criteria
Versions- 1,2,3	INCLUSION	INCL02	CLL requiring treatment according to the IWCLL criteria
Versions- 4,5	INCLUSION	INCL02	CLL that requires treatment according to the IWCLL criteria
Versions- 1,2,3,4,5	INCLUSION	INCL03	Total CIRS score > 6 or CrCl < 70 mL/min
Versions-1,2,3,4	INCLUSION	INCL04	Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as follows, unless cytopenia is due to marrow involvement of CLL: Absolute neutrophil count $\geq 1.0 \times 10^9/L$ Platelet counts $\geq 30 \times 10^9/L$; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator); platelet count should be $\geq 10 \times 10^9/L$ if there is bone marrow involvement

Standards matter



Doing now what patients need next