

Why and What Standards for Oncology Studies (Solid Tumor, Lymphoma and Leukemia)?

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ABSTRACT

Each therapeutic area has its own unique data collection and analysis. Oncology especially, has particularly specific standards for collection and analysis of data. Oncology studies are also separated into one of three different sub types according to response criteria guidelines. The first sub type, Solid Tumor study, usually follows RECIST (Response Evaluation Criteria in Solid Tumor). The second sub type, Lymphoma study, usually follows Cheson. Lastly, Leukemia study follows study specific guidelines (IWCLL for Chronic Lymphocytic Leukemia, IWAML for Acute Myeloid Leukemia, NCCN Guidelines for Acute Lymphoblastic Leukemia and ESMO clinical practice guides for Chronic Myeloid Leukemia).

This paper will demonstrate the notable level of sophistication implemented in CDISC standards, mainly driven by the differentiation across different response criteria. The paper will specifically show what SDTM domains are used to collect the different data points in each type. For example, Solid tumor studies collect tumor results in TR and TU and response in RS. Lymphoma studies collect not only tumor results and response, but also bone marrow assessment in LB and FA, and spleen and liver enlargement in PE. Leukemia studies collect blood counts (i.e., lymphocytes, neutrophils, hemoglobin and platelet count) in LB and genetic mutation as well as what are collected in Lymphoma studies. The paper will also introduce oncology terminologies (e.g., CR, PR, SD, PD, NE) and oncology-specific ADaM data sets - Time to Event (--TTE) data set.

Finally, the paper will show how standards (e.g., response criteria guidelines and CDISC) will streamline clinical trial artefacts development in oncology studies and how end to end clinical trial artefacts development can be accomplished through this standards-driven process.

INTRODUCTION OF ONCOLOGY CLINICAL TRIAL STUDIES

Oncology studies are complex and difficult for programmers and statisticians to conduct since oncology studies demand different way of collecting, measuring and analyzing data. Oncology studies are different from other studies in the following area.

- Tumor measurements and their response to drug
- Oncology-specific measurements for response criteria (e.g., Liver and Spleen Enlargement, Bone Marrow Infiltrate and Blood Counts)
- Oncology-diagnosis measurements (e.g., immunophenotype, performance status on ECOG, staging)
- Toxicity (Lab and AE)
- Time to Event Analysis (e.g., OS, PFS, TTP and ORR)

There are three types of oncology clinical trial studies.

- Solid Tumor
- Lymphoma
- Leukemia Response

The solid tumor studies usually follow RECIST 1.0 or 1.1 on tumor response evaluation criteria. Lymphoma studies usually follow Cheson 1997 or 2007. Leukemia studies have four different types and each type follow different response evaluation criteria - Acute Lymphoblastic Leukemia (ALL) following National Comprehensive Cancer Network (NCCN) Guideline verions1 2012, Acute Myeloid Leukemia (AML) following IWAML 2003, Chronic Lymphocytic Leukemia (CLL) following IWCLL 2008, Chronic Myeloid Leukemia (CML) following CML ESMO Guideline. This paper will use Chronic Lymphocytic Leukemia as an example. In addition, immunotherapy follow irRC (immune related RECIST) 2008.

ONCOLOGIC SPECIFIC CDISC STANDARDS

CDISC recently developed Oncology-related standards both in SDTM, ADaM and Control CT.

SDTM

- TU: Tumor Identification
- TR: Tumor Results
- RS: Response

ADaM

- ADTTE: Time to Event ADaM datasets

CT

- Response Criteria
 - CR – Complete Response
 - PR – Partial Response
 - SD – Stable Disease
 - PD – Progression Disease
 - NE – Not Evaluable
 - NonCR/NonPD - Non Complete Response/Non Progressive Disease
- Tumor Measurements
 - LDIAM – Longest Diameter
 - SUMDIA – Sum of Diameter
 - LPERP – Longest perpendicular of Diameter
 - AREA – Area
 - SUMAREA – Sum of Area
 - TUMSTATE – Tumor State
- Response
 - TRGRESP – Target Response
 - NTRGRESP – Non-target Response
 - NEWLPROG – New Lesion Progression
 - OVRLRESP – Overall Response
 - BESTRESP – Best Response

SOLOID TUMOR DATA COLLECTION AND SDTM IMPLEMENTATION

INTRODUCTION OF SOLID TUMOR

Solid Tumor are masses of abnormal tissue that originate in organs or soft tissues that typically do not include fluid areas and cysts (e.g., breast cancer, liver cancer, pancreatic cancer and melanoma)

INTRODUCTION OF RECIST

RECIST is Response Evaluation Criteria in Solid Tumor and there are two versions- 1.0 and 1.1. Most recent studies follow the recent version, RECIST 1.1, released on October 2008. The paper will follow RECIST 1.1.

SOLID TUMOR SPECIFIC MEASUREMENT

A lesion is any abnormality in the tissue of an organism and can be described as a cut, an injury, an infected area or a tumor. In oncology study, lesions are tumors. They are divided into three types for the purpose of their measurements.

- Target lesions
- Non-target lesions
- New lesions

TARGET LESIONS

In clinical trials following RECITS 1.1, target lesions selection at baseline follows as

- Measurable
- 5 lesions total
- Maximum of 2 lesions per organ
- Representing all involved organs
- Quantitative measurements
 - Longest diameter of lesions
 - Short axis of Lymph nodes
 - Sum of diameters (both lesions and lymph nodes)

NON TARGET LESIONS

Non-target lesions selection at baseline follows as

- All other lesions beside target lesions
- Qualitative measurements – present, absent or unequivocal progression.

NEW LESIONS

New lesions at post-baseline follows as

- Any lesions that are newly found at post-baseline.
- Either quantitative or qualitative measurements

RESPONSE ASSESSMENT AT GIVEN VISIT ACCORDING TO RESIST 1.1

A response of the drug at given cycle will be determined by the followings.

- SUMDIA of target lesions (TR)
- Non-target lesions assessment (TR)
- New lesions (TR)

Examples of response assessment at give visit according to RECIST 1.1 are introduced in Table 1 and 2.

Table 1 - SDTM TR (Tumor Response) dataset

USUBJID	TRGRID	TRLINKID	TRTESTCD	TRTEST	TRORES	TRORESU	VISIT
001-01-001	Target	T01	LDIAM	Longest Diameter	10	mm	Cycle 1
001-01-001	Target	T02	LDIAM	Longest Diameter	10	mm	Cycle 1
001-01-001	Target	T03	LDIAM	Longest Diameter	15	mm	Cycle 1
001-01-001	Target		SUMDIAM	Sum of Diameter	35	mm	Cycle 1
001-01-001	Non-Target	NT01	TUMSTATE	Tumor State	PRESENT		Cycle 1
001-01-001	Non-Target	NT02	TUMSTATE	Tumor State	PRESENT		Cycle 1
001-01-001	Non-Target	NT03	TUMSTATE	Tumor State	PRESENT		Cycle 1

Table 2 - SDTM RS (Response) dataset

USUBJID	RSTESTCD	RSTEST	RSCAT	RSORRES	VISIT
001-01-001	TRGRESP	Target Response	RECIST 1.1	PR	Cycle 1
001-01-001	NTRGRESP	Non-target Response	RECIST 1.1	NonCR/NonPD	Cycle 1
001-01-001	NEWLPROG	New Lesion Progression	RECIST 1.1	N	Cycle 1
001-01-001	OVRLRESP	Overall Response	RECIST 1.1	PR	Cycle 1

Key points to note in the table 1 and 2 are:

- Row 4 of table 1 determines row 1 of table 2
- Row 5 to 8 of table 1 determines row 2 of table 2
- No indication of new lesion of table 1 determines row 3 of table 2
- In table 2, row 1 to 3 will determine row 4.

LYMPHOMA DATA COLLECTION AND SDTM IMPLEMENTATION

INTRODUCTION OF LYMPHOMA

Lymphoma is cancer that starts in lymph node.

INTRODUCTION OF CHESON

An international working group (IWG) published guidelines for response measurements on non-Hodgkin's Lymphoma (NHL) in 1999. In 2007, Cheson 2007 was published with the recommendations from other lymphoma studies and with the addition of more advanced diagnosis.

LYMPHOMA SPECIFIC MEASUREMENT

In lymphoma clinical trials, lesions are enlarged lymph nodes, nodal masses and extra nodal masses, and a lymph node lesion is considered measurable if its length of longest diameter is greater than 15 mm or that of its greatest perpendicular axis is greater than 10 mm by CT scan.

Lymphoma studies following Cheson 2007 will collect the following measurements.

- Tumor measurements in CT / MRI
- Lymph Node, Nodal Masses and Extra Nodal Masses
- PET scan on lesions (to distinguish viable tumor from fibrosis)

- Bone Marrow Assessment
- Spleen and Liver Enlargement Assessment

SDTM IMPLEMENTATION ON CHESON 2007 MEASUREMENT

Cheson 2007 measurements are implemented in follow SDTM domains.

- Tumor measurement in SPD by CT SCAN (TR)
- Tumor assessment by PET (TR)
- Bone Marrow Infiltrate (LB and FA)
- Spleen and Liver Enlargement (PE)

These measurements will be assessed to determine a response(RS) at each cycle.

LEUKEMIA DATA COLLECTION AND SDTM IMPLEMENTATION

INTRODUCTION OF LEUKEMIA

Leukemia is a cancer that usually begins in the bone marrow and result in high numbers of abnormal white blood cells(lymphocytes).

There are four types of Leukemia:

- Acute Lymphoblastic Leukemia(ALL) - a rapid increase in the number of immature white blood cells.
- Acute Myeloid Leukemia (AML) - a rapid increase in the number of abnormal white blood cells in bone marrow that interfere with the production of normal blood cells.
- Chronic Lymphocytic Leukemia (CLL) - excessive buildup of relatively mature, but still abnormal, white blood cells
- Chronic Myeloid Leukemia (CML) - the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood.

The paper will focus only on CLL and the progress of CLL follows as.

1. Mutation of stem cells in bone marrow
2. Abnormal WBC (CLL cells) are formed
3. CLL cells increase in bone marrow
4. CLL cells increase in blood

INTRODUCTION OF IWCLL

An international workshop on chronic lymphocytic leukemia (IWCLL) group published guidelines for response measurements on CLL in 1996 and 2008.

IWCLL 2008 defines the diagnosis of CLL.

- Blood: $> 5 \times 10^9$ B lymphocytes/L (5000 / uL) in blood.
- Immunophenotype (flow cytometry) of Lymphocytes:
 - A presence of T-cell antigen CD5
 - A presence of B-cell surface CD19, CD20, CD23
 - Low surface immunoglobulin CD20, CD79b

LEUKEMIA SPECIFIC MEASUREMENT

The following will be collected according to IWCLL 2008.

- Tumor measurements in CT / MRI – Lymph Node
- Blood Lymphocytes
- Bone Marrow Assessment
- Spleen and Liver Enlargement Assessment
- Blood Count Assessment – Neutrophils, Platelets and Hemoglobin
- Immunophenotype (flow cytometry)
- Performance Status by ECOG (Eastern Cooperative Oncology Group)
- Staging – Assessment of disease progress for treatment plan
 - Rai: 0 (low risk), 1 & 2 (intermediate risk), 3 (high risk)
 - Binet: A, B, C

Immunophenotype, ECOG and staging measurements are considered additional since they don't determine response at each cycle.

SDTM IMPLEMENTATION ON IWCLL 2008 MEASUREMENT

IWCLL 2008 measurements are implemented in follow SDTM domains.

- Tumor measurement in SPD by CT SCAN (TR)
- Bone Marrow Infiltrate (LB and FA)
- Spleen and Liver Enlargement (PE)
- Blood Counts (LB)

These measurements will be assessed to determine a response at given visit.

ONCOLOGY SPECIFIC ENDPoins AND TIME-TO-EVENT ADAM IMPLEMENTATION

The most common efficacy end points in oncology studies are

- OS (Overall Survival)
 - Primary
 - Time from randomization until death
 - Intent-to-treat population
- PFS (Progression Free Survival)
 - Primary
 - Time from randomization until objective tumor progression or death
 - Death is NOT censored.
 - Often the preferred end points in lymphoma studies (i.e., incurable histologic subtypes).
- TTP (Time to Progression)
 - Time from randomization until objective tumor progression
 - Death is censored.
- ORR (Objective Response Rate)
 - Rate of partial and complete responses to non-responses.
 - Until 1970s, FDA usually approved cancer drugs based on ORR.
 - Usually used in Phase II trials of novel new agents.
- Response Duration
 - Time from CR or PR until relapse or progression

ORR, DFS, PFS, TTP, ORR and Response Duration are based on tumor assessments. The oncology specific endpoints are expressed in ADaM Time to Event datasets as in Table 3.

Table 3 - ADTTE dataset with Progression Free Survival (PFS) parameter

USUBJID	TRTP	PARAM	AVAL	STARTDT	ADT	CNSR	EVNTDESC
001-01-001	Study Drug	Progression Free Survival (Days)	452	2011-01-01	2011-03-01	0	PROGRESSIVE DISEASE
001-01-002	Control	Progression Free Survival (Days)	338	2011-02-01	2011-01-05	1	LOST OT FOLLOW-UP
001-01-003	Control	Progression Free Survival (Days)	212	2011-02-05	2011-09-05	0	DEATH
001-01-004	Study Drug	Progression Free Survival (Days)	463	2011-03-20	2012-06-25	1	COMPLETED
001-01-005	Study Drug	Progression Free Survival (Days)	67	2011-03-26	2011-06-01	0	PROGRESSIVE DISEASE

Key points to note in the table 3 is:

- Row 1, 3, 5 are NOT censored.

STANDARDS DRIVEN ONCOLOGY STUDIES

ONCOLOGY SPECIFIC STANDARDS

The paper introduces oncology specific standards.

- Response Criteria guidelines
 - RECIST 1.1
 - Cheson 2007
 - IWCLL 2008
- Data Collection
 - Tumor measurement
 - Bone Marrow Assessment

- Spleen and Liver Enlargement Assessment
- Blood Counts
- Response Assessment
- CDISC
 - SDTM: TU, TR, RS
 - ADaM: -- TTE
 - CT: CR, PR, PD, SD, LDIAM, SUMDIA, LPERP, AREA, SUMAREA, TUMSTATE TRGRES, NTRGRES, NEWLPROG
- Analysis: OS, PFS, TTP, ORR, DFS

Since we are able to standardize response criteria guidelines, data collection, SDTM, ADaM and Analysis, we can create oncology-specific end to end clinical trial artefacts development process. As seen in Figure 1, Lymphoma studies will select standards from each process and those interlinked standards will create standards in the next process. So, oncologic specific standards can drive clinical trial artefacts from protocol, collection, SDTM, ADaM and analysis.

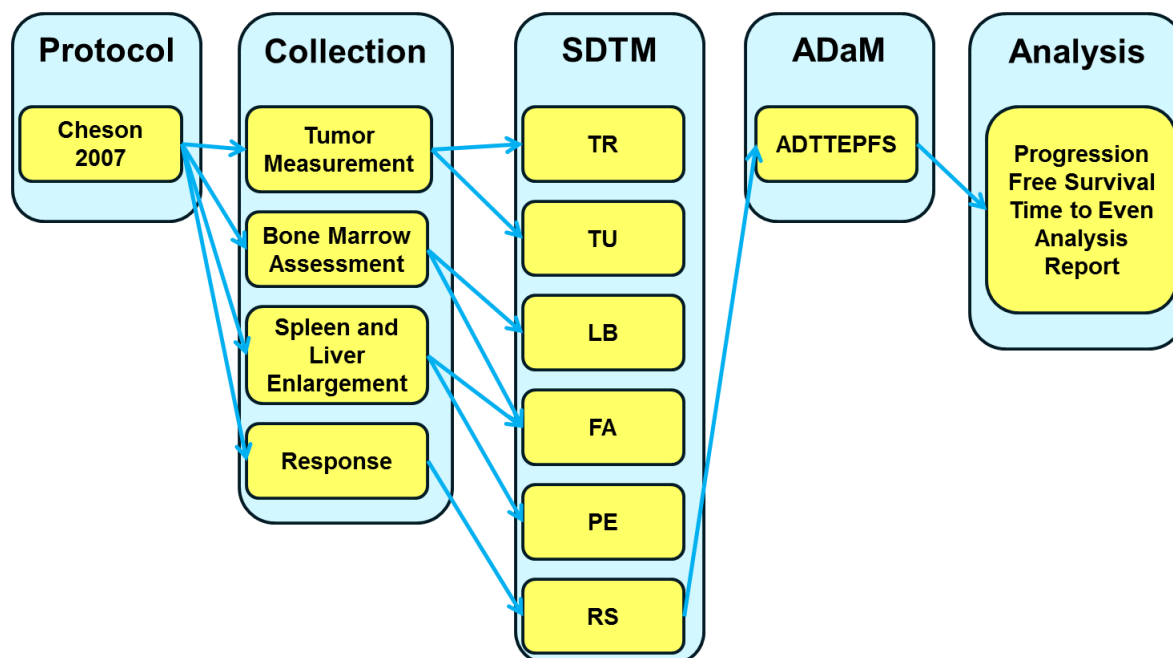


Figure 1. End to End Standards-driven Lymphoma Studies

CONCLUSION

CDISC introduces the new tumor domains in SDTM and Time to Event datasets in ADaM, but it is also very important for programmers and statisticians to understand therapeutic characteristics and methods in Oncology. Response criteria such as RECIST 1.1, Cheson 2007, IWCLL 2008 introduce how to collect oncology specific data and analyze responses in oncology studies. The combination of response criteria and CDISC can streamline the end to end standards-driven oncology clinical trial process.

REFERENCES

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- Revised Response Criteria for Malignant Lymphoma (Cheson 2007)
- Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines (IWCLL 2008)
- ADaM Implementation Guide, Version V 1.0 (ADaMIG v1.0)
- Analysis Data Model, Version 2.1 (ADaM 2.1)
- ADaM Basic Data Structure for Time-to-Event Analyses
- SDTM Version 1.3
- SDTM Implementation Guide Version 3.2
- CDER Guidance for Industry – Clinical Trial Endpoints for the approval of Cancer Drugs and Biologics

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