PHUSE 2017

RG08

The impact of Regulations on Immuno-Oncology Submissions

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ABSTRACT

The clinical study report, submission data and analysis data are all impacted by existing regulations intended to streamline communication between sponsors and regulatory agencies. However, when these regulations were initially created they could not anticipate the detail that would be required for immuno-oncology studies. With the advances in antibody technologies sponsors are rapidly adopting these new biological entities with existing small molecules and other treatments to address a variety of cancers. This adds complexity for all parties involved. A few examples should bring light to the idiosyncrasies arising from possible interpretations of these regulations, highlighting ICH, RECIST and CDISC.

INTRODUCTION

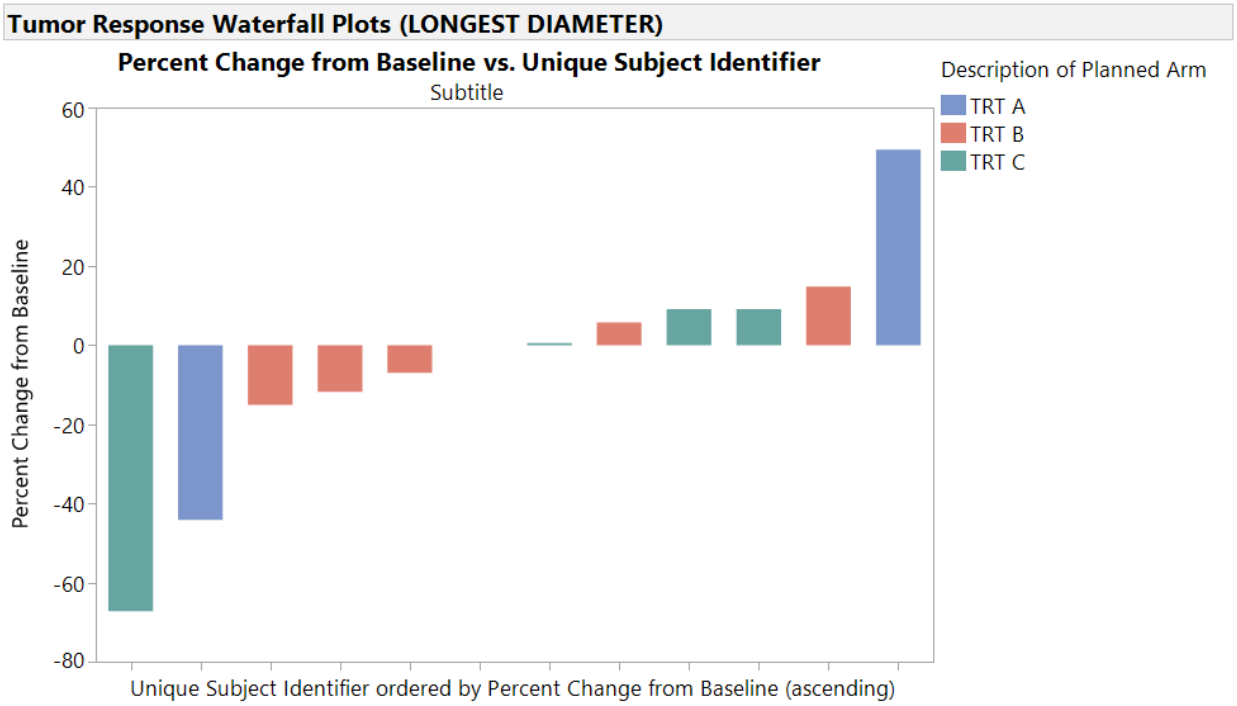
Immuno-Oncology studies add to the complexity of clinical trials. Many of the more recent studies involve multiple study drugs, often combining a monoclonal antibody with a chemotherapeutic agent to elicit improved immunogenicity for tumors. The Response Evaluation Criteria In Solid Tumors (RECIST), which provide rules by which cancer patients are determined to be improving, staying the same or worsening, would often fail for immuno-oncology studies whose criteria differ slightly as the action of immunotherapeutic agent is often delayed. These outcomes require different efficacy data, typically captured in the SDTM domains TU, TR and RS. Reports and analyses are created from these and other domains and included in the Clinical Study Report (CSR). Clinical data scientists rely heavily on changes from baseline of the Tumor Response domain with ancillary data provided primarily by the Demographics and Disposition domains. Three visualizations are presented which indicate the progression of the disease, Waterfall Plots, Spaghetti Plots and Swimmer Plots. Finally, a mock narrative shows the safety side of the CSR.

WATERFALL PLOTS

Waterfall Plots are very useful for indicating Percent Change from Baseline calculations on the individual level. This view allows each subject to be evaluated based on the treatment they receive to determine if their tumors are growing, shrinking or staying the same. The Waterfall Plot in this example is relatively simple in that it combines information from fewer domains than the others in this paper. Whether the values increase, decrease or stay the same indicate progressive disease (PD), complete or partial response (CR/PR) or no change respectively. The following SDTM variables are used when creating this report:

Category of Question
Name of Measurement, Test or Examination
Unique Subject Identifier
Percent Change from Baseline (derived)
Study Identifier
Visit Number
Visit Name
Date/Time of Collection
Study Day of Collection
Domain Abbreviation

Subject Identifier for the Study
Subject Reference Start Date/Time
Subject Reference End Date/Time
Study Site Identifier
Date/Time of Birth
Age
Age Units
Sex
Race
Ethnicity
Planned Arm Code
Description of Planned Arm
Country



SPAGHETTI PLOTS

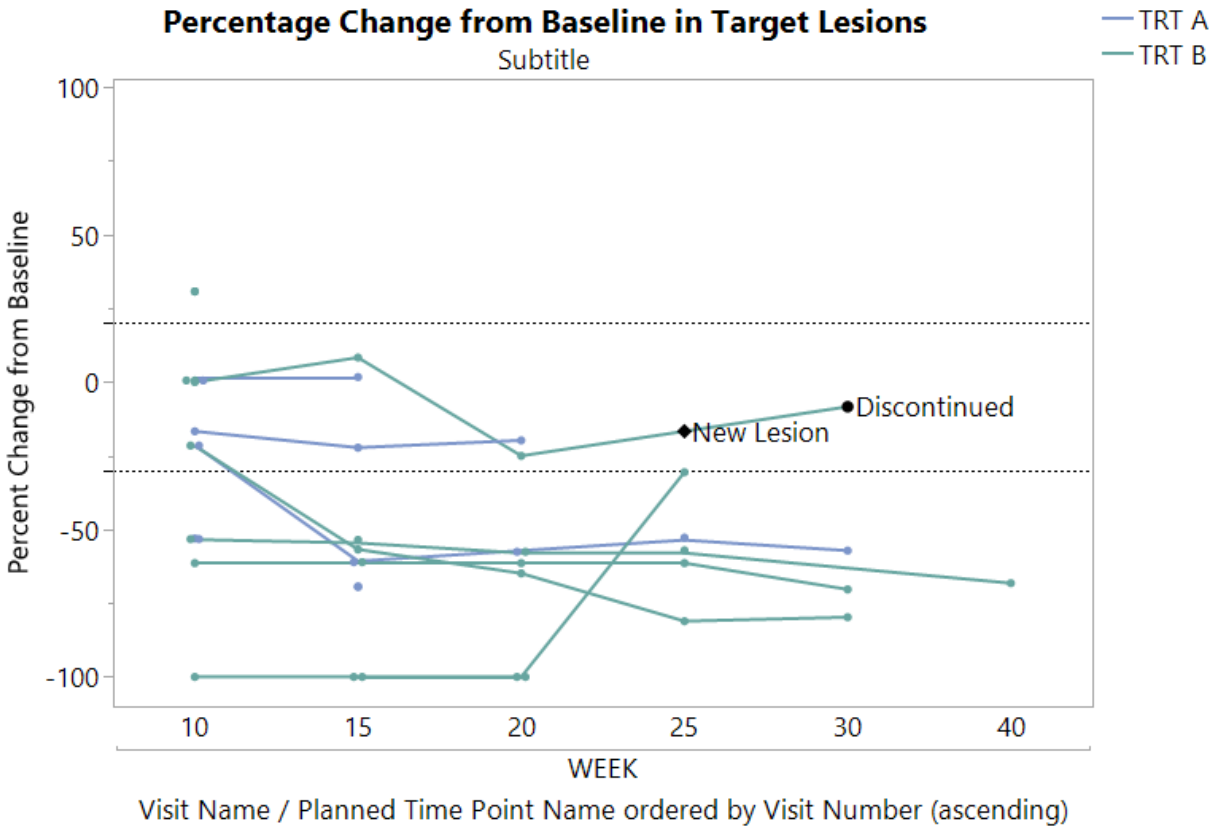
Spaghetti Plots raise the level of sophistication as the changes from baseline can be measured over time. By combining the tumor domains TR and RS merged with Disposition and Demographics Domains. In order to more completely understand the disease progression it is useful to highlight discontinuation from study drug as well as the occurrence of new lesions. In order to facilitate this view, the following SDTM and derived variables are listed below:

Unique Subject Identifier
Visit Number
Visit Name
Planned Time Point Number
Planned Time Point Name
LONGDIA_1 (derived)

PERLODIA_1 (derived)
Study Identifier
Domain Abbreviation
Subject Identifier for the Study
Subject Reference Start Date/Time
Subject Reference End Date/Time
Study Site Identifier

Date/Time of Birth
Age
Age Units
Sex
Race
Ethnicity
Planned Arm Code
Description of Planned Arm

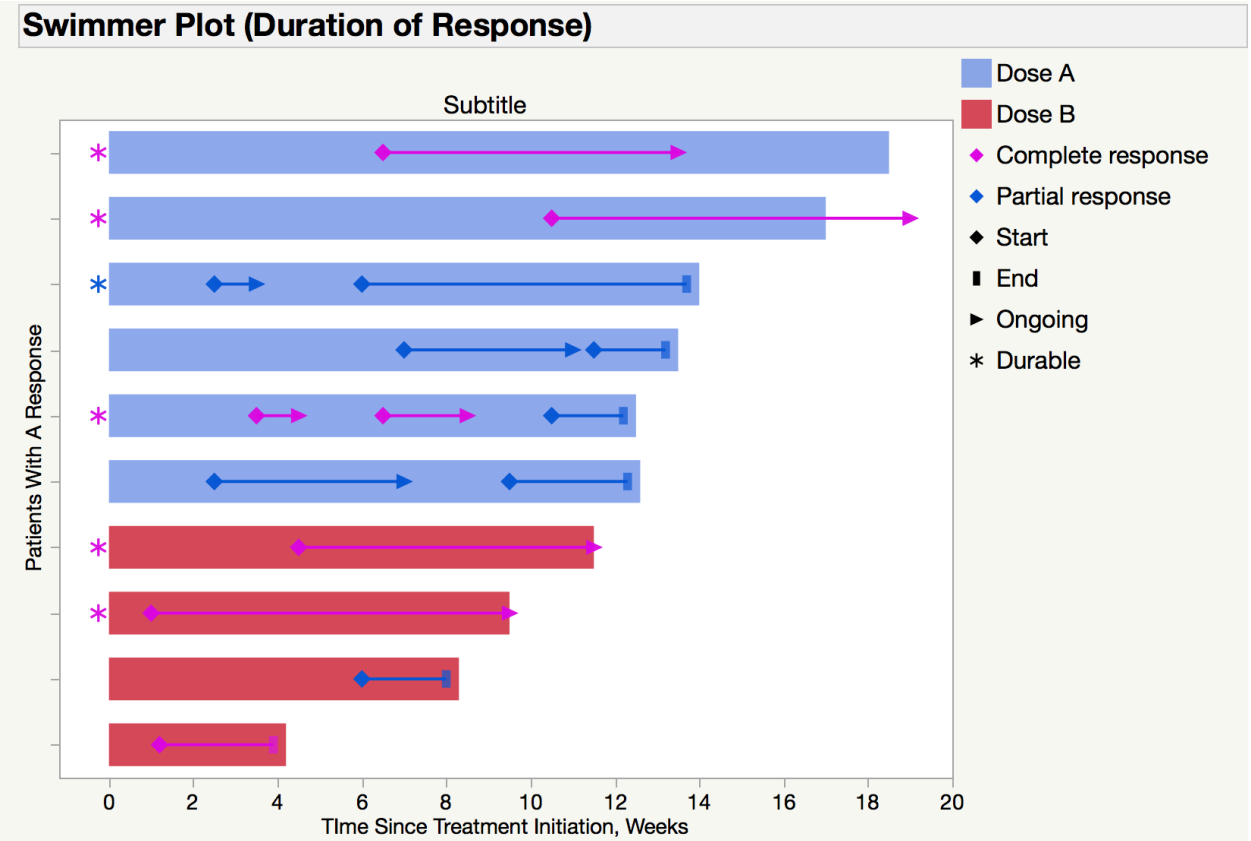
Country
Date/Time of Collection
Study Day of Collection
Study Day of Start of Disposition Event
Category for Disposition Event
Subcategory for Disposition Event
DSWK (derived)
DSSTWK (derived)



SWIMMER PLOTS

Swimmer Plots are used to indicate the duration of patient response time on different treatment regimes. There are numerous variables in SDTM used to create the Swimmer Plots as they are are merged from TR, RS, DS and DM. See the following list of SDTM variables used to generate the graph below:

Unique Subject Identifier
Subject Reference Start Date/Time
Subject Reference End Date/Time
Study Identifier
Domain Abbreviation
Sequence Number
Sponsor-Defined Identifier
Short Name of Measurement, Test or Exam
Response Assessment/Test
Category of Question
Subcategory for Question
Result or Finding in Original Units
Character Result/Finding in Std Format
Completion Status
Reason Not Performed
Method of Test or Examination
Vendor Name
Radiologist or Reader
Visit Number
Visit Name
Date/Time of Assessment
Study Day
Planned Time Point Name
Planned Time Point Number
STDY
errdtSTDY (derived)
partial_RSDTC (derived)
ENDY
RSENDY
errdtENDY (derived)
RSENDTC
partial_RSENDTC (derived)
RSDUR
LOG2_RSDUR (derived)
RSWK (derived)
Category for Disposition Event
Subcategory for Disposition Event
Date/Time of Collection
Start Date/Time of Disposition Event
Study Day of Visit/Collection/Exam
Study Day of Start of Disposition Event
DSWK (derived)
DSSTWK (derived)
Subject Identifier for the Study
Study Site Identifier
Date/Time of Birth
Age
Age Units
Sex
Race
Ethnicity
Planned Arm Code
Description of Planned Arm
Country
Date/Time of Collection 2
Study Day of Collection
errdtRFDY (derived)
partial_rfendtc (derived)
RFDY (derived)
RFWK (derived)
Epoch
Start Date/Time of Visit
End Date/Time of Visit
Study Day of Start of Visit
Study Day of End of Visit
Description of Unplanned Visit
partial_SVSTDTC (derived)
partial_SVENDTC (derived)
SVDUR
LOG2_SVDUR (derived)
SVENWK (derived)
end
start
ResponseWK
Complete
Ongoing


Swimmer Plot (Duration of Response)
Subtitle
Patients With A Response
TIme Since Treatment Initiation, Weeks
0
2
4
6
8
10
12
14
16
18
20
Dose A
Dose B
Complete response
Partial response
Start
End
Ongoing
Durable

SERIOUS ADVERSE EVENT NARRATIVES

Serious adverse event narratives provide a key part of the safety story for subjects on immuno-oncology trials. They are more complex than the typical trial as the patients are often on multiple drugs for which outcomes, causality and actions must be accounted for each treatment. Added complexity exists in the medications as well as current medications received and prior cancer therapies are included. The data populating these narratives resides throughout the SDTM data model and creates a comprehensive overview of each patient. Medical Writers can augment these as they see fit. An example of a narrative generated for an oncology study from the following SDTM variables is shown below:

	DSEPOCH	CMTRT
USUBJID	HODECOD	CMSTDTC
AGE	HOSTDTC	CMENDTC
RACE	MHOCCUR	DSDECOD
SEX	CMOCCUR	DSSTDTC
RFSTDTC	DSENDY	DSCAT
AESTDTC	HOSTDY	EXDOSE
AEENDTC	HOENDY	EXDOSU
AEDECOD	COUNTRY	EXTRT
AETERM	STUDYID	EXSTDTC
AESTDY	SUBJID	EXENDTC
CMTRT	AEACNXXX	LBTRTEM
AESER	AEACNYYY	LBDTC
MHTERM	AEOUTXXX	LBTESTCD
LBTESTCD	AEOUTYYY	LBTEST
ACTARM	AERELXXX	LBSTRESN
AEACNOTH	AERELYYY	LBBLFL
AECONTRT	AEDECOD	LBORRESU
AESCAN	AETOXGR	LBNRIND
	AESEQ	LBSTNRHI

Protocol Identification:	ONCOLOGY STUDY
Subject identification/Country:	09012017 (USA)
Investigation Product/Cohort/Route:	SASIMAB and JMPIMAB/ONE/INTRAVENOUS
Date of first dose:	09APR2001
Date of last dose:	09MAY2002
TESAE (Preferred Term):	headache/09JUN2001
TESAE(Preferred Term):	phlebitis/05JUN2001
TESAE(Preferred Term):	haemorrhage/02JUL2000
TESAE(Preferred Term):	pyrexia/26MAY2000

Narrative

Subject 09012017, a 49-year-old Caucasian male received 300 mg/kg SASIMAB and 10 mg/kg JMPIMAB / 10 mg/kg SASIMAB (S1) - Expansion. The subject's past medical history included abdominal pain(grade 2), fatigue (grade 1), phlebitis (grade 1), nausea (grade 1), hypertension

(grade 1), high cholesterol(grade 1), and hypertension(grade 2). The subject is a non-smoker.

The subject was diagnosed with Melanoma on 03NOV2000 with non-metastatic lymph nodes. At study entry, the subject's cancer was stage 2 and ECOG performance status was: 1. Previous anticancer therapy included CHEMOTHERAPY/XXXX from 02MAR1998 through 18APR1998, CHEMOTHERAPY/BBBB from 19AUG1999 through 07OCT1999, SURGERY/YYY from 24FEB2000 through 24FEB2000.

On 09JUN2000 (Day 42) the subject experienced headache that was (Grade 3) in severity. The last dose of SASIMAB and JMPIMAB prior to the event onset was administered on 27MAY2000. Concurrent with this event that occurred within a +/- 7-day window of the onset of the SAE included phlebitis (Grade 3), pyrexia (Grade 2), … Concomitant medications taken 7 days before the onset of the SAE up to 30 days following onset included: vitamin d3*, vitamin b*, simvastatin*, maxeran*, ...

The subject was discharged on 12JUN2000 and the adverse event was considered recovered/resolved on 12JUN2000. The event was 3 days in duration and SASIMAB was NONE and JMPIMAB was NONE due to this event. The investigator considered the AE to be NOT RELATED to SASIMAB and NOT RELATED to JMPIMAB.

…

Relevant laboratory findings included:
…

NOTE TO AUTHOR: …

Re-CHALLENGE/De-CHALLENGE: …

NOTE TO AUTHOR: DEATH: On 16JUL2003, 679 days after starting study drug(s) and 10 days after permanently discontinuing study drug(s), the subject died.

CONCLUSIONS

Comprehensive, reproducible guidance (RECIST/irRECIST/ICH) and standards (CDISC) can propel science to a pace where the frequency of improvements in clinical trials increases. This is already apparent by the number of immuno-oncology trials currently in progress. The review of these drugs alone would overwhelm the industry and regulatory agencies without these standards in place. Combined with improvements in diagnostic capabilities cancer patients will benefit greatly from these advances in science.

REFERENCES

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3. FDA, "FDA Guidance for Industry Clinical Trail Endpoints for the Approval of Cancer Drugs and Biologics," 2007.
4. EMA, "Guideline on the evaluation of anticancer medicinal products in man," 2013.
5. NJ Pandya, "Waterfall Charts in Oncology Trials - Ride the Wave," in PharmaSUG, 2012.
6. CDISC, "SDTM version 3.1.3," 2013.

ACKNOWLEDGEMENTS

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RECOMMENDED READING

ICHE3 Structure and Content of Clinical Study Reports
RECIST
SDTM Version 1.3
SDTM Implementation Guide 3.1.3
SDTM Supplement Tumor Domains

CONTACT INFORMATION

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