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SDTM and Analysis Tips for Oncology Combo Trials with Concurrent Chemoradiotherapy

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ABSTRACT

Oncology combination trials that involve concurrent chemoradiotherapy (cCRT) often have complicated study designs due to the involvement of multiple therapeutic types with varying dosing schedules. Consequently, the complexity of such trials presents several challenges when it comes to applying SDTM and analysis methods effectively.

This paper provides insights into SDTM and analysis tips specifically tailored for oncology combo trials with concurrent chemoradiotherapy based on our experience. These tips cover topics such as the data mapping methods of exposure for different components of treatment**,** drug switch and the deriving rule for determining treatment duration for study drugs with varying dosing schedules.

INTRODUCTION

Over the years, the combined administration of both chemotherapy and radiotherapy as an anticancer treatment has become an established treatment for a diverse range of locally advanced solid tumors, especially the combination of cCRT and immunotherapy has emerged as an exciting field of research with the potential for significant clinical benefit. Therefore, we are more likely to encounter oncology combo trials that use the design of investigational products with concurrent chemoradiotherapy. The involvement of multiple therapeutic types with varying dosing schedules leads to complex study designs and complicated scenarios, which also pose challenges for programmers when it comes to applying SDTM and analysis rules efficiently. Which domain should we map the radiotherapy data to? How can we handle the scenario of chemotherapy with drug switch? What should we take into consideration when calculating the treatment duration of components with different strategies in administration? We will take an oncology combo trial with cCRT as the sample, and find out our experience and tips for the questions.

DESCRIPTION OF THE SAMPLE TRIAL

The intervention of the sample trial has 2 main components: investigational product X and concurrent chemoradiotherapy. The chemotherapy involves 3 drugs, Y, cisplatin and carboplatin, and the protocol designed: if cisplatin is contraindicated or not tolerated, carboplatin may be used.

Intervention	Frequency	Route
X	Day 1 of each cycle (3-week cycles)	Intravenously
Y	Days 1, 2, and 3 of each cycle (3-week cycles)	Intravenously
Cisplatin / Carboplatin	Day 1 of each cycle (3-week cycles)	Intravenously
Radiotherapy	Once daily	

Table 1 Intervention of The Sample Trial

SDTM TIPS

There are 2 most significant differences of this sample trial: radiotherapy is one component of protocol-specified study treatment, and there might be drug switch scenario of cisplatin and carboplatin. How will they affect us in data tabulation?

MAPPING RADIOTHERAPY DATA

Intuitively, it makes sense to map data related to radiotherapy into the PR domain. Additionally, in the SDTMIG PR Assumptions, radiotherapy is cited as one of the examples of therapeutic procedures. However, this is not the only method to handle radiotherapy data, as we should consider the protocol and study design in the first place.

Per the SDTMIG v3.4, EX is an interventions domain that contains the details of a subject's exposure to protocol-specified study treatment, and the EC domain model reflects protocol-specified study treatment administrations as collected. Be aware of the “protocol-specified”, we should take it into consideration when choose which domain to tabulate the data. It might be common sense to map protocol-specified chemotherapy into exposure domains, so how about radiotherapy in oncology trials with concurrent chemoradiotherapy? It is also a protocol-specified study treatment.

In our practice, if chemotherapy and/or radiotherapy is one of study treatments, data from CRF forms of chemotherapy and/or radiotherapy will also be mapped to EC as well. Otherwise, they will be mapped into CM for chemotherapy and PR for radiotherapy. Even in the same study, “prior radiotherapy” and “radiotherapy regimen of protocol-specified study treatment” will go to different domains, PR for the former and Exposure domains to the latter.

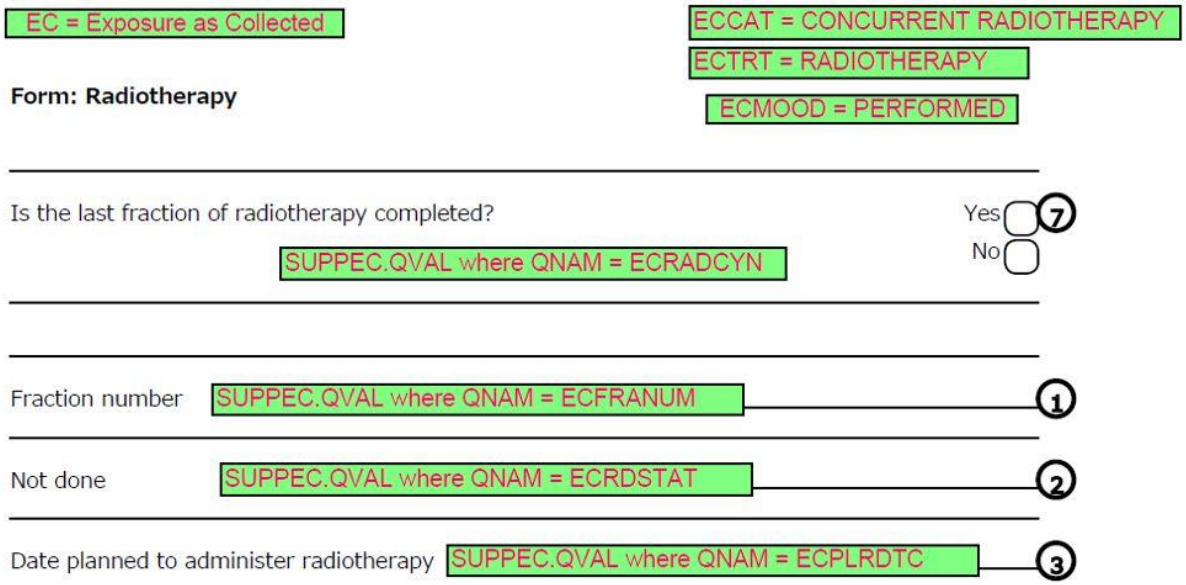

Figure 1 Sample Annotations of Form "Radiotherapy"

HANDLING OF DRUG SWITCH SCENARIO

A complicate study design may include a drug switch. Drug switch is defined as the replacement of a patient’s prescribed drug with a similar drug from a different manufacturer or a drug of same type. This can happen when the original drug is no longer available or when the patient experiences side effects from the original drug. For example, a study treatment has chemotherapy regimen, and designed as when cisplatin is contraindicated or not tolerated, carboplatin may be used.

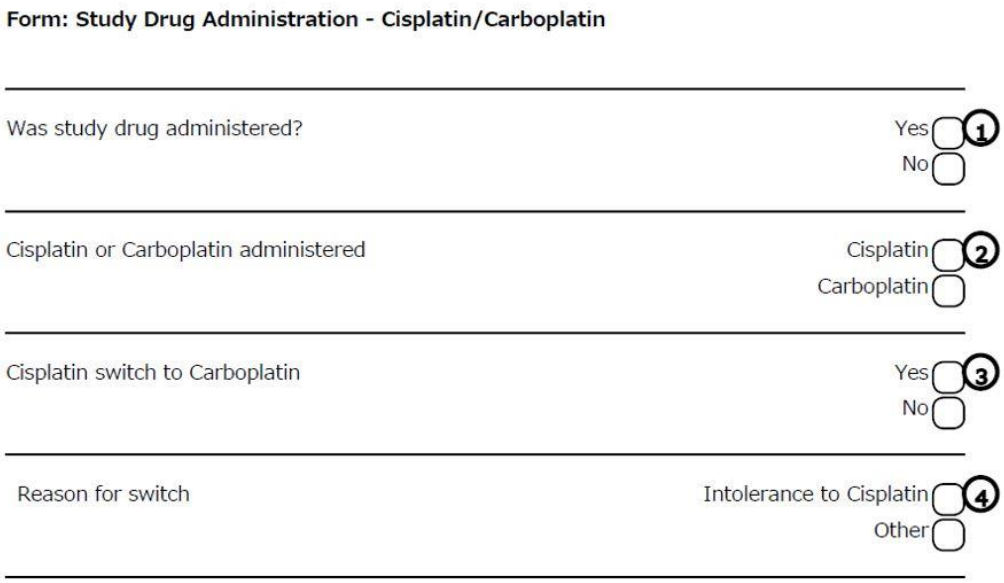

Figure 2 Sample Form of Drug Switch

As other drug components of study treatment, the form shows a leading question of “Was study drug administered”. When choose “Yes”, the data collection system will show other exposure related questions, such as which drug administered, dose, start and end date, etc. When choose “No”, system will direct the collector to reason for dose missed and so on. However, it will skip the question of which drug administered, as there is no such administration.

This leads to a question for programmers, how should we handle ECTRT for these no drug administered records? In our practice, below method is more recommended, which is following ALCOA requirements, convenient for further analysis and satisfies the SDTMIG: we map the combination of drug names in this chemotherapy regimen with switch scenario, and put the exact name of each administered drug to SUPPEC domain.

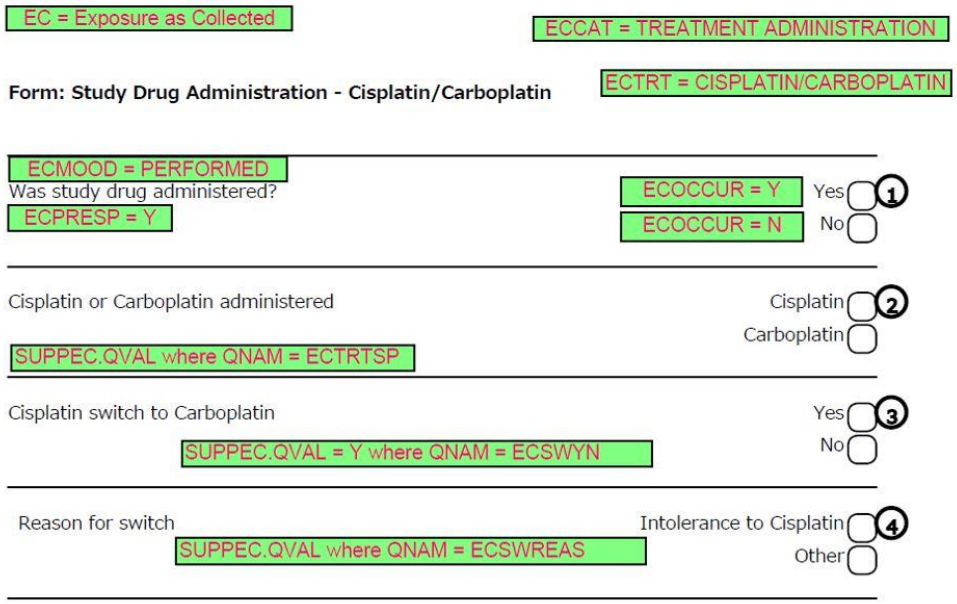

Figure 3 Sample Annotations of Form of Drug Switch

There might be other design types of CRF or unique features of data collection system. Try to figure out the inner logic, it will lead you to the best solution in that scenario.

ANALYSIS TIPS FOR CALCULATING TREATMENT DURATION

After mapping the exposure data properly to SDTM domains, the requirement of analysis is waiting for us. Treatment Duration (TD) is the most common analysis object, and will always be calculated as last date of exposure - first dose date + 1. The first dose date is collected, and the last date of exposure will be identified per various scenarios, in consideration of cutoff date, death date, treatment cycle and treatment status.

It is a straightforward algorithm when drug(s) administered every day, but how about treatments designed with drug(s) administered on specific day or several days in each cycle? For our sample trial, the intravenous plan of drug X and Y have different strategies for each cycle (3 weeks), below is the algorithms of them:

Drug	**Algorithm - Treatment Ongoing**	**Algorithm -Treatment Discontinuation**
X (intravenously on Day 1)	cutoff date – first dose date + 1	min (cutoff date, death date, last dose date + 20) – first dose date + 1
Y (intravenously on Days 1, 2, and 3)	cutoff date – first dose date + 1	min (cutoff date, death date, first dose date in last cycle + 20) – first dose date + 1

Table 2 Algorithms of Different Drugs

Let us interpret the rule for Drug X and Y, especially the numbers added to last dose date/ first dose date in last cycle. Our deriving rules should reflect the actual study drug administration situation, so it is unreasonable using the exact last dose date or first date in last cycle, which means not taking the remain non-administration part of the cycle into account, and causes a large reduction of duration comparing to the reality. Actually, the logic of choosing number to add in Drug X and Y are the same – we consider the first date in last cycle as a start symbol of last cycle (for Drug X, last dose date is also the first date in last cycle), and complete the duration of last cycle by adding the remain part of it, equal to cycle length - 1.

As we all know, the reality is always more complex than imagination, and the doses missed/delay are almost certain events in a study. The limitation of deriving rule in former section comes out when doses delay in last cycle Day 2 or 3 of Drug Y. There also might be other algorithms, such as last dose date + 18 (cycle length – continuous days of administration) or last dose date + (cycle length – last dose day in cycle). They all have their own accuracy in particular angle and limitations. Figure out the focus of your project and company, there must be a suitable one.

CONCLUSION

There is no best solution for all scenarios, but might be a proper solution for your project and company. Keep the guidance and requirements of authorities in mind, figure out the inner logic of data, aim for the authenticity of analysis. The complicated study designs would not be treacherous canyon for programmers.

REFERENCES

Kathrine S Rallis, Thomas Ho Lai Yau, Michail Sideris. 2021. “Chemoradiotherapy in Cancer Treatment: Rationale and Clinical Applications” Anticancer Research, 41 (1) 1-7.

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RECOMMENDED READING

- Study Data Tabulation Model (SDTM) v2.0
- Study Data Tabulation Model Implementation Guide (SDTMIG) v3.4

CONTACT INFORMATION

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