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Navigating Statistical Programming Challenges in Early Phase Oncology Trials

Dandan Du, BeiGene (Beijing) Co., Ltd.

ABSTRACT

With innovative study designs emerging and being widely applied, early phase oncology trials, which focus on evaluating the safety and toxicity profiles of investigational drugs or therapies in a limited patient cohort, are increasingly presenting challenges not only in trial operation and management but also in statistical programming. Common challenges in these trials include: 1) Characterizing, identifying, and reporting adverse events of special interest (AESI), and 2) Defining evaluable analysis set for dose-limiting toxicity (DLT) assessment. Moreover, unique challenges arise in the data analysis and interpretation on patients who switch drugs during the trial. This paper examines these three challenges encountered in routine statistical programming tasks within early phase oncology trials and explores practical solutions.

INTRODUCTION

Clinical trials are generally categorized into four phases: Phase I, Phase II, Phase III, and Phase IV. Early phase clinical trials, which include Phase I and non-randomized Phase II trials, represent the initial steps in assessing the safety, tolerability, and preliminary efficacy of a new medical intervention. These trials involve a small group of healthy volunteers or patients and aim to determine the optimal dosage and administration regimen for the intervention.

In early phase oncology trials, innovative study designs like dose-escalation studies, adaptive designs, and phase I / II combine trials are commonly applied to maximize efficiency and gather essential data with minimal participant involvement. Due to the nature of these studies, staff involved in trial operation and management, as well as statistical programming in early phase oncology trials may encounter distinctive challenges. A typical challenge is that early phase oncology trials often have tight timelines. The Safety Monitoring Committee (SMC), one of the most common deliveries, often needs update monthly. Thus, delivering results promptly while balancing multiple priorities, placing pressure on statistical programmers.

Additionally, statistical programmers often face challenges, such as 1) Characterizing, identifying, and reporting adverse events of special interest, and 2) Defining evaluable analysis set for dose-limiting toxicity assessment. In this paper, we also address another unique challenge arising from the situation that patients switch drugs during the trial.

ADVERSE EVENTS OF SPECIAL INTEREST

Based on Council for International Organizations of Medical Sciences (CIOMS) Working Group VII, the definition of adverse event of special interest (AESI) was described as[1]:

"An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted."

The ICH Topic E2F development safety update report (DSUR) - Scientific guideline also emphasized the importance of identifying AESIs[2]:

"If important and appropriate, the report should also include adverse reactions of special interest within the line listings and adverse events of special interest in summary tabulations. The basis for selection of such events/reactions should be explained."

Monitoring and reporting of AESIs is crucial for assessing the safety profile of a compound in early phase oncology trials. However, mastering the skills of characterizing, identifying, and reporting AESI can present a challenge for programmers.

CHARACTERIZING OF AESI

In an early phase oncology trial, AESIs are often predefined in protocol, based on factors such as the drug's mechanism of action, preclinical toxicity data, and known safety concerns from similar compounds in previous studies experiences and existing literatures evidence. It's important to clearly define the types of events to be considered AESIs, criteria for severity and attribution, and methods for data collection and reporting in the protocol design.

IDENTIFICATION OF AESI

Identifying AESI is an adjudication process that engages multiple functional groups. Initially, the safety team will generate a spreadsheet of potential AESIs by searching MedDRA dictionary. The medical team will then review the spreadsheet to determine whether an AE added in the spreadsheet should be flagged as an AESI.

Based on specific emphasis and previous AE occurrences, the AESI MedDRA AE list provided by other teams often varies across different analyses, which posing a challenge for statistical programmers in following analysis steps. Here, we propose a streamlined solution where programmers only need to update the lookup table.

For the following statistical programmer's process: we transfer the spreadsheet into a SAS dataset to serve as a lookup table for ADAE.

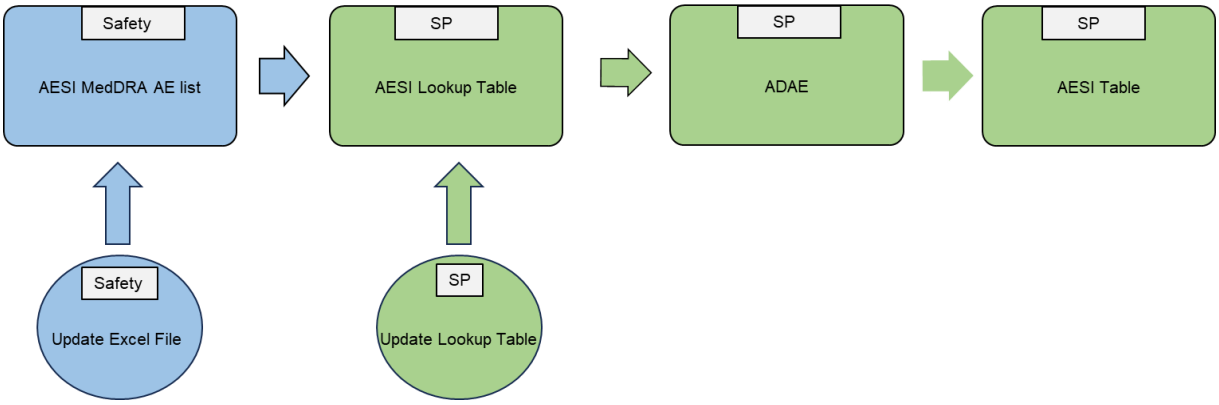


Figure 1. AESI Process

During this process, the primary task for programmers is to merge the AE dataset with AESI terms using Standardized MedDRA Queries (SMQs) and/or Customized MedDRA Queries (CMQs). SMQs are extracted from MedDRA using collection of PTs and are helpful for detecting safety signals associated with established clusters of adverse event terms, while CMQs are customized to identify specific adverse events that may be of interest within company, therapeutic area, project, etc.

All submitted SMQs and CMQs need to be indicated in analysis dataset ADAE. The following variables are examples from CDISC ADaM Occurrence Data Structure (OCCDS)[3].

Variable Name	Variable Label	Type	Codelist / Controlled Terms	Core	CDISC Notes
SMQzzNAM	SMQ zz Name	Char		Cond	The standardized MedDRA queries name. Would be blank for terms that are not in the SMQ. Therefore this variable could be blank for all records if no terms within the study were included in the SMQ. Conditional on whether SMQ analysis is done.
SMQzzCD	SMQ zz Code	Num		Perm	The standardized MedDRA queries number code.
SMQzzSC	SMQ zz Scope	Char	BROAD, NARROW	Cond	The search strategy for SMQs can be narrow or broad. The preferred terms that are narrow in scope have high specificity for identifying events of interest while the broad terms have high sensitivity. By definition, all narrow terms are also considered within the broad scope. Therefore, to summarize all broad terms, terms with either narrow OR broad would be considered. Will be null for terms that do not meet the criteria. Conditional on whether SMQ analysis is done.
SMQzzSCN	SMQ zz Scope (N)	Num	1, 2	Perm	Will be null for terms that do not meet the criteria.
CQzzNAM	Customized Query zz Name	Char		Cond	The customized query (CQ) name or name of the AE of special interest category based on a grouping of terms. Would be blank for terms that are not in the CQ. Conditional on whether CQ analysis is done. Examples: "DERMATOLOGICAL EVENTS" "CARDIAC EVENTS", "IARS (INFUSION ASSOCIATED REACTIONS)"

Table 1. Standardized MedDRA Query Variables

Here is an illustration of the adverse events analysis dataset (ADAE) defined above.

Key points to note in the example are:

1. Row 2 and Row 4: same AEDECOD, same SMQ name.

2. Row 1 and Row 5: different AEDECOD, same SMQ name.

3. Row 1 and Row 5: same SMQ name, different CQ Names.

Row	USUBJID	AEDECOD	SMQ01NAM	SMQ01CD	SMQ01SC	SMQ02NAM	SMQ02CD	SMQ02SC	CQ01NAM	CQ02NAM	CQ03NAM	MEDDRAV
1	ABC-001	Dizziness	SMQ1	20000001	BROAD				CQ1			MedDRA 24.0
2	ABC-001	Fever				SMQ2	20000002	NARROW				MedDRA 24.0
3	ABC-001	Headache								CQ2		MedDRA 24.0
4	XYZ-001	Fever				SMQ2	20000002	NARROW				MedDRA 24.0
5	XYZ-001	Nause	SMQ1	20000001	BROAD						CQ3	MedDRA 24.0

Table 2. Sample ADAE Dataset contains SMQ and CMQ

REPORTING OF AESI

Since AESIs are typically identified at a compound level, consistency in reporting AESIs is essential across all clinical trials within the same compound.

Unlike AEs which are commonly summarized by SOC and/or PT, AESIs are typically identified through the term groups of SMQs and/or CMQs per medical condition to reflect a risk category.

The following are example tables of adverse events summarized by a specific SMQ or CMQ and the grouping PTs.

SMQ1

	Cohort 1 (N = xx) n (%)	Cohort 2 (N = xx) n (%)	Total (N = xx) n (%)
Any SMQ1 (Broad) Event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dizziness	xx (xx.x)	xx (xx.x)	xx (xx.x)
Nause	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2	xx (xx.x)	xx (xx.x)	xx (xx.x)

SMQ2

	Cohort 1 (N = xx) n (%)	Cohort 2 (N = xx) n (%)	Total (N = xx) n (%)
Any SMQ2 (Narrow) Event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Fever	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT3	xx (xx.x)	xx (xx.x)	xx (xx.x)

CQ1

	Cohort 1 (N = xx) n (%)	Cohort 2 (N = xx) n (%)	Total (N = xx) n (%)
Any CQ1 Event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Dizziness	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT4	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT5	xx (xx.x)	xx (xx.x)	xx (xx.x)

Table 3. Example of Summary of SMQ / CMQ Adverse Events by Actual Treatment Group

DOSE-LIMITING TOXICITY

Dose-limiting toxicity refers to the maximum level of adverse effects that a patient can tolerate from study drugs or treatments without becoming too harmful or dangerous and leads to restriction of further dose escalation. The definition varies across different trials, but generally includes death related to study intervention, >= grade 3 non-haematological, or >= grade 4 haematological toxicity[4].

Phase I oncology trials primarily aim to determine the recommended dosage of an investigational drugs for subsequent evaluation. One common endpoint is dose-limiting toxicities (DLT), a key index to evaluate the maximum tolerated dose (MTD) and recommended dose (RD) of a new drug. Typically, consecutive cohorts of patients receive escalating doses until a predetermined dose-limiting toxicity is observed.

HOW TO DEFINE DLT EVALUABLE ANALYSIS SET?

Assessing and evaluating DLT is often based on predefined criteria in protocol, which may vary among different trials due to differences in drug mechanisms and administration routes. These variations often involve distinct evaluation periods and criteria for evaluable eligibility, posing a challenge for statistical programming.

When defining DLT evaluable analysis set, several factors should be taken into consideration:

DLT Observation Period

The DLT observation period is the duration after a specific dose level is administered to patients in each cohort, monitoring is required to determine if a DLT event has occurred.

Most conventional cytotoxic chemotherapy drugs are administrated intermittently and periodically. The DLT observation period for dose-escalation will be set as the first drug cycle, typically 21 days or 28 days for many standard regimens. The period varies depending on the drug's pharmacokinetics and expected onset of toxicities. Drugs with shorter half-lives are metabolized and eliminated from the body more rapidly, DLTs may manifest sooner after administration compared to drugs with longer half-lives. Therefore, a DLT observation period of 7 days or 14 days may be sufficient. For drugs with acute toxicities, assessments may occur within a relatively short timeframe after administration. In contrast, for drugs with delayed toxicities or longer treatment cycles, the observation period may extend beyond 28 days, such as 42 days or longer, to capture late-onset adverse events and cumulative toxicities more comprehensively.

For molecularly targeted agents (MTAs), toxic effects often occur late after treatment initiation, only taking cycle 1 as observation period may not be appropriate.

Due to hysteresis effect, immunological therapy also needs a long assessment period.

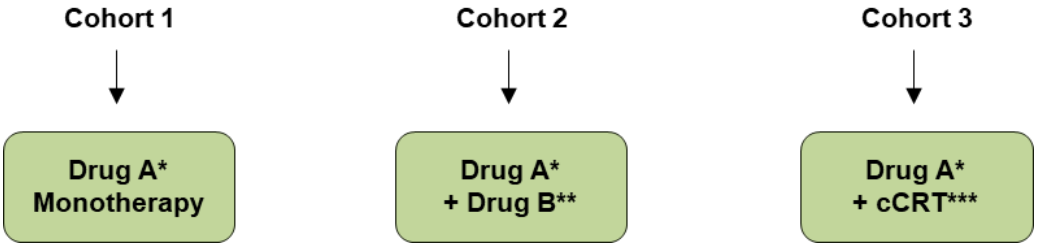
Relative Dose Intensity

Relative dose intensity (RDI) is defined as the ratio of the actual dose intensity received to the planned dose intensity. It helps evaluate whether patients are receiving treatment as planned and can offer insights into treatment effectiveness and potential outcomes. Experts in drug development have a consensus that an RDI threshold exceeding 75% of the intended dosage is acceptable[4].

Different from monotherapy, patients enroll in combo therapy will be considered evaluable for DLTs if they receive >= XX% RDI of each scheduled study drugs administration during the DLT assessment window and remain on study throughout the DLT period.

Drugs with different administration routes, including oral drug, injection drug, radiotherapy, etc. may have different RDI criteria for DLT assessment.

Here is a study design which patients are randomized into 3 cohorts:



*Drug A: administered orally.

**Drug B: chemotherapy, intravenous infusion.

***cCRT (concurrent chemoradiotherapy): Drug B+ Radiotherapy

Figure 2. Study Design with Multiple Cohorts

In Cohort 1 and Cohort 2, patients will be considered evaluable for DLTs if they receive the RDI criteria >= 80% of each scheduled study drug(s) administration during the DLT assessment window (28 days).

In comparison to other cohorts, combined radiotherapy and chemotherapy may lead to increased toxicity and reduced patient tolerance. Therefore, a different threshold was set for Cohort 3: patients will be considered evaluable for DLTs if they receive the RDI criteria >= 60% of each scheduled study drug(s) administration during the DLT assessment window (42 days).

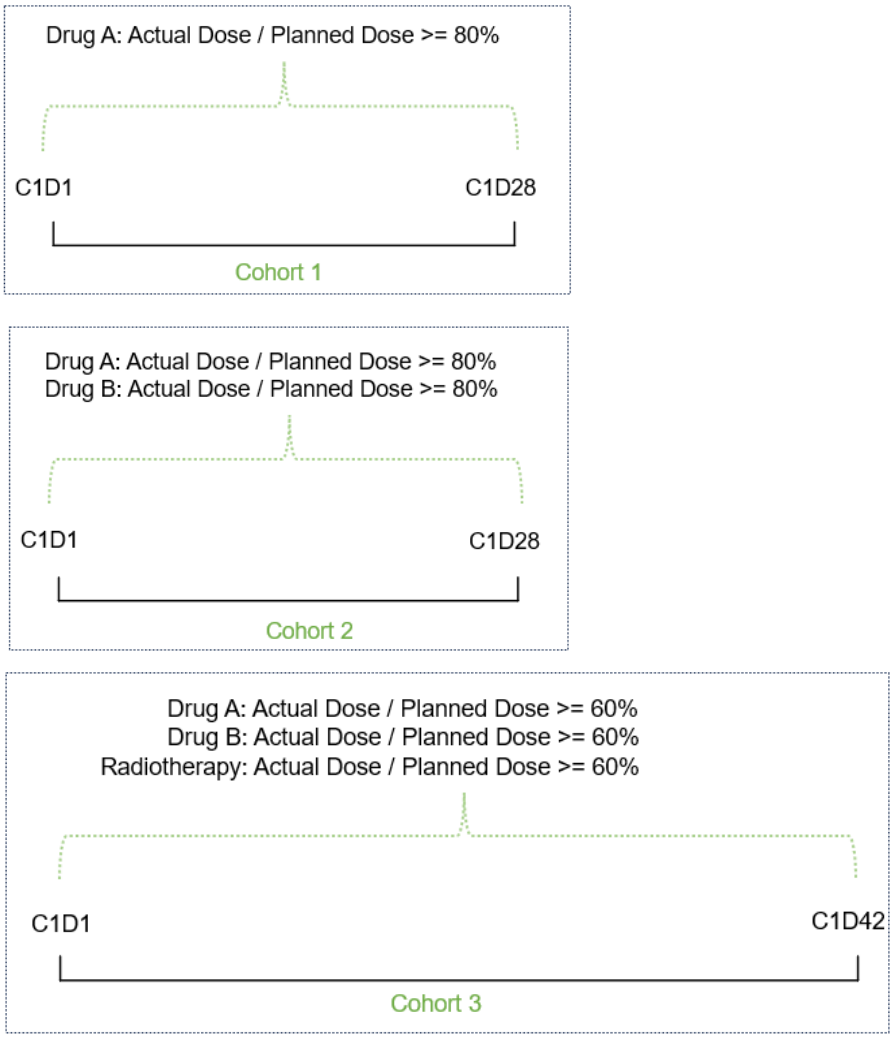


Figure 3. DLT Assessment Requirement by Cohort

Other Requirements

Patients should be observed for a period following the administration of the treatment. Safety assessments during this observation period involve monitoring patients for any adverse reactions or side effects to ensure the treatment's safety profile. As per the protocol's schedule, safety assessments typically include AE evaluation, physical examination, vital signs monitoring, ECOG performance status assessment, laboratory tests, etc. For statistical programmer, verifying whether patients have completed required safety assessments during the DLT observation period poses a challenge. It's crucial to specify which tests are pertinent for programming.

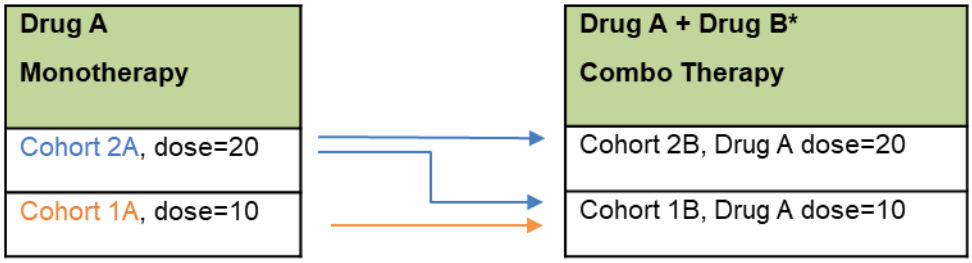
Additionally, there are some other exceptional situations. In instances where programming cannot confirm certain criteria, the study team may need to provide an adjudication list for programming reference. Patients using prohibited concomitant medications/procedures or those with protocol deviations may need to be excluded. Furthermore, numerous special situations may arise that cannot be predefined.

DRUG SWITCH

THE DEFINITION OF DRUG SWITCH

Drug switch refers to the process of transitioning a patient from one treatment regimen to another during the study. It occurs commonly due to safety concerns, efficacy considerations, logistical issues, protocol amendments, or patient preferences.

Here is a typical study design include drug switch:



*Drug B: standard medicine.

Figure 4. Study Design of Drug Switch

Patients in arm Drug A Monotherapy whose disease progresses on Drug A may be given the option to switch to Combine Therapy of Drug A and Drug B, and should meet below criteria:

- Disease progression is demonstrated radiographically or via clinical symptoms.
- Switching to combination therapy of Drug A and Drug B will not occur until Cohort 1B or Cohort 2B has been determined to be safe and tolerable.
- Drug A dose depending on the monotherapy dose level of Drug A they have been receiving by the time of disease progression.
- Drug A dose not higher than that have been determined to be tolerable by the SMC.

STUDY SCHEDULE

When patients undergo a drug switch, the planned study schedule may be altered:

- Drug A Monotherapy maintains the study schedule and Schedule of Assessments before, during, and after the transition to the combination of Drug A + Drug B.
- For patients who switch the treatment following disease progression, the disease status upon disease progression will be established as the “new baseline” for tumor assessment. Subsequent tumor response evaluation should be based on the “new baseline” scan from the initiation of the new study treatment.
- There are two scenarios of tumor assessments that we may encounter.

  All subsequent tumor assessments should still be conducted according to the planned schedule until study treatment discontinuation.

  or

  Subsequent imaging should be based on the new “baseline” scan, tumor imaging will be performed every 8 weeks (± 7 days) for the first 24 weeks then every 12 weeks (± 14 days), from Day 1 of the new treatment.

* New D1: Day 1 of the new treatment.

Figure 5. Image Schedule before / after Switch

DATA COLLECTION

For patients who are enrolled in Drug A Monotherapy cohort:

If 'overall response' under 'Response Assessments' folder is 'Progressive disease', 'Re-consent and Treatment through progression' CRF will be triggered, to collect the switch status and to which treatment arm they transitioned. Then if 'Name of the treatment subject agreed to take' is selected as 'Combination Therapy of Drug A and Drug B, it means that the patient experiences a 'switch therapy'.

Form: Response Assessment

Overall response	Complete response ☐
	Progressive disease ☐

Form: Re-consent and Treatment through progression

Did the subject consent to continue taking study drug after disease progression?	Yes ☐
	No ☐
Name of the treatment subject agree to take	Drug A Monotherapy ☐
	Combination Therapy of Drug A and Drug B ☐

Figure 6. Sample Form of Drug Switch

Also, we should ensure that the accurate recording of drug information during both the Drug A Monotherapy period and the Drug A + Drug B Combo Therapy period.

Meanwhile, the ‘Response Assessment Summary-Rebaseline’ reflects the exact timepoint of ‘new baseline’, overall response is ‘Progressive disease’. ‘Response Assessments-Post Disease Progression’ folder will be triggered to facilitate future tumor assessment: subsequent assessments should be based on ‘new baseline’ and can be distinguished from prior assessments.

DATA ANALYSIS

How does a drug switch affect data analysis?

ADaM datasets are inherently analysis ready. It is crucial to ensure that drug switch related information is properly flagged and managed within the ADaM datasets if we need to acquire analysis difference before and after switch.

ADaM datasets may be impacted:

- ADSL

Below table lists the primary variables related to drug switch in ADSL dataset.

Dataset Name	Variable Name	Variable Label	Variable Type	Origin / Source / Method / Comment
ADSL	USUBJID	Unique Subject Identifier	Char	DM.USUBJID
ADSL	ARM	Description of Planned Arm	Char	Initial assigned cohort.
ADSL	TRT01P	Planned Treatment for Period 01	Char	Subject-level identifier that represents the planned treatment for period 01.
ADSL	TRT02P	Planned Treatment for Period 02	Char	Subject-level identifier that represents the planned treatment for period 02.
ADSL	TRT01A	Actual Treatment for Period 01	Char	The actual cohort. Subject-level identifier that represents the actual treatment for the subject for period 01.
ADSL	TRT02A	Actual Treatment for Period 02	Char	The actual cohort. Subject-level identifier that represents the actual treatment for the subject for period 02.
ADSL	EOSDT	End of Study Date	Num	Date subject ended the study - date of completion or date of discontinuation.
ADSL	DTHDT	Date of Death	Num	Date of subject's death. Derived from DM.DTHDTC.
ADSL	DCUTDT	Data Cutoff Date	Num	Set to 31DEC2001
ADSL	TR01SDT	Date of First Exposure in Period 01	Num	Date of First Exposure in Period 01
ADSL	TR01EDT	Date of Last Exposure in Period 01	Num	Date of Last Exposure in Period 01
ADSL	TR02SDT	Date of First Exposure in Period 02	Num	Date of First Exposure in Period 02, this variable is the date of first exposure to the switched drug treatment.
ADSL	TR02EDT	Date of Last Exposure in Period 02	Num	Date of Last Exposure in Period 02, this variable is the date of last exposure to the switched drug treatment.
ADSL	AP01SDT	Period 01 Start Date	Num	Set to TR01SDT
ADSL	AP01EDT	Period 01 End Date	Num	If TR02SDT =. (No drug switch occurs): AP01EDT = Min (EOSDT, DTHDT, DCUTDT). Else if not missing TR02SDT (Drug switch occurs): AP01EDT = TR02SDT - 1.
ADSL	AP02SDT	Period 02 Start Date	Num	If TR02SDT =. (No drug switch occurs): AP02SDT =. Else if not missing TR02SDT (Drug switch occurs): AP02SDT = TR02SDT
ADSL	AP02EDT	Period 02 End Date	Num	If TR02SDT =. (No drug switch occurs): AP02EDT =. Else if not missing TR02SDT (Drug switch occurs): AP02EDT = Min (EOSDT, DTHDT, DCUTDT).

Table 4. Example of ADSL Variable Metadata

Below table illustrates the treatment variables for 3 patients. Note that patient 1002 switched from Drug A Monotherapy cohort to Drug A + Drug B Combo Therapy cohort.

Row	USUBJID	ARM	TRT01P	TRT02P	TRT01A	TRT02A	EOSDT	DTHDT	DCUTDT
1	1001	Drug A	Drug A		Drug A				31DEC2001
2	1002	Drug A	Drug A	Drug A+Drug B	Drug A	Drug A+Drug B	01OCT2001		31DEC2001
3	1003	Drug A+Drug B	Drug A+Drug B		Drug A+Drug B			01SEP2001	31DEC2001

Row	TR01SDT	TR01EDT	TR02SDT	TR02EDT	AP01SDT	AP01EDT	AP02SDT	AP02EDT
1 (cont)	01JAN2001	01MAR2001			01JAN2001	31DEC2001		
2 (cont)	01JAN2001	01MAR2001	01APR2001	10JUN2001	01JAN2001	31MAR2001	01APR2001	01OCT2001
3 (cont)	01JAN2001	01MAR2001			01JAN2001	01SEP2001		

Table 5. Drug Switch – ADSL Dataset

- ADAE

Definition of treatment-emergent adverse events (TEAEs):

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days after study drug(s) discontinuation or initiation of a new anticancer therapy, whichever occurs first.

For patients who switch to Drug A and Drug B Combo Therapy, when we derive TEAE, we should make it clear of the date of last exposure to any protocol required therapy in the entire study. In some circumstances, we may derive TEAE per different period separately.

Below table lists the primary variables related to drug switch in ADAE dataset.

Dataset Name	Variable Name	Variable Label	Variable Type	Origin / Source / Method / Comment
ADAE	TRTA	Actual Treatment	Char	Set to TRT01A if ASTDT is within the 1st period: [ADSL.AP01SDT<= ADAE.ASTDT<=ADSL.AP01EDT]; Set to TRT02A if ASTDT is within the 2nd period: [ADSL.AP02SDT<=ADAE.ASTDT<=ADSL.AP02EDT].
ADAE	ASEQ	Sequence Number	Num	AE.AESEQ
ADAE	AEDECOD	Dictionary-Derived Term	Char	AE.AEDECOD
ADAE	ASTDT	Analysis Start Date	Num	Convert AESTDTC into numeric date when all 3 components are present (day, month, year).
ADAE	APERIOD	Period	Num	If ADSL.TR01SDT <= ADAE.ASTDT <= ADSL.TR01EDT then APERIOD=1, else if ADSL.TR02SDT <= ADAE.ASTDT <= ADSL.TR02EDT then APERIOD=2.
ADAE	APERIODC	Period (C)	Char	Record-level timing variable that represents the analysis period (Original period/After drug switch) within the study associated with the record for analysis purposes. If APERIOD=1 then APERIODC=' ORIGINAL', else if APERIOD=2 then APERIODC=' SWITCH'.
ADAE	TRTEMFL	Treatment Emergent Analysis Flag	Char	If ADSL.TR01SDT <= ADAE.ASTDT <= (ADSL.TR01EDT+30) or ADSL.TR02SDT <=ADAE. ASTDT <= (ADSL.TR02EDT+30) then TRTEMFL=Y.

Table 6. Example of ADAE Variable Metadata

In below table: Row 3 and Row 4 are AE records of patient 1002 who switched from Drug A Monotherapy cohort to Drug A + Drug B Combo Therapy cohort. AE in Row 3 occurred before switch (in period 1), and AE in Row 4 occurred after switch (in period 2).

Row	USUBJID	ARM	TRT01A	TRT02A	TRTA	ASEQ	AEDECOD	ASTDT
1	1001	Drug A	Drug A		Drug A	1	VOMITING	01JAN2001
2	1001	Drug A	Drug A		Drug A	2	PHARYNGITIS	01DEC2001
3	1002	Drug A	Drug A	Drug A+Drug B	Drug A	1	FEVER	01MAR2001
4	1002	Drug A	Drug A	Drug A+Drug B	Drug A+Drug B	2	HEADACHE	10APR2001
5	1003	Drug A+Drug B	Drug A+Drug B		Drug A+Drug B	1	HEADACHE	01FEB2001
6	1003	Drug A+Drug B	Drug A+Drug B		Drug A+Drug B	2	CONSTIPATION	01MAR2001

Row	AP01SDT	AP01EDT	AP02SDT	AP02EDT	APERIOD	APERIODC	TR01SDT	TR01EDT	TR02SDT	TR02EDT	TRTEMFL
1 (cont)	01JAN2001	31DEC2001			1	ORIGRIN	01JAN2001	01MAR2001			Y
2 (cont)	01JAN2001	31DEC2001			1	ORIGRIN	01JAN2001	01MAR2001			
3 (cont)	01JAN2001	31MAR2001	01APR2001	01OCT2001	1	ORIGRIN	01JAN2001	01MAR2001	01APR2001	10JUN2001	Y
4 (cont)	01JAN2001	31MAR2001	01APR2001	01OCT2001	2	SWITCH	01JAN2001	01MAR2001	01APR2001	10JUN2001	Y
5 (cont)	01JAN2001	01SEP2001			1	ORIGRIN	01JAN2001	01MAR2001			Y
6 (cont)	01JAN2001	01SEP2001			1	ORIGRIN	01JAN2001	01MAR2001			Y

Table 7. Drug Switch – ADAE Dataset

- ADRS

With a new baseline established for switched patients, assessments conducted after the switch may need to be excluded.

DATA INTERPRETATION AND REPORTING

Drug switching during an early phase oncology trial can have significant implications for data analysis and interpretation, presenting considerable challenges in statistical programming, particularly in analysis reporting.

Per our study design, 2 patients enrolled in Drug A Monotherapy cohort, and 1 patient enrolled Drug A + Drug B Combo Therapy cohort initially. And 1 patient in Drug A Monotherapy cohort switch to Drug A + Drug B Combo Therapy cohort.

Depends on different analysis request and proportion of switch patients, below 2 scenarios may exist in real time analysis:

- Ignore switch situation and keep the original cohort when category subgroup.
- Make summary per different period separately. As displayed in below patient disposition table and AE count table, which devide patients and events by period without causing confusion.

Period 1

	Drug A Monotherapy (N = 2)	Drug A + Drug B Combo Therapy (N = 1)	Total (N = 3)
Number of Patients Treated, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Patients Discontinued From Treatment, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Discontinuation, n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Progressive disease	xx (xx.x)	xx (xx.x)	xx (xx.x)

Period 2

	Drug A + Drug B Combo Therapy (N = 1)
Number of Patients Treated, n (%)	xx (xx.x)
Number of Patients Discontinued From Treatment, n (%)	xx (xx.x)
Reason for Discontinuation, n (%)	xx (xx.x)
Adverse event	xx (xx.x)
Progressive disease	xx (xx.x)

Table 8. Patient Disposition and Reasons for Discontinuation by Period

Period 1

	Drug A Monotherapy (N = 2)	Drug A + Drug B Combo Therapy (N = 1)	Total (N = 3)
Patients With at Least One TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
	xx (xx.x)	xx (xx.x)	xx (xx.x)
SOC1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT1	xx (xx.x)	xx (xx.x)	xx (xx.x)
PT2	xx (xx.x)	xx (xx.x)	xx (xx.x)

Period 2

	Drug A + Drug B Combo Therapy (N = 1)
Patients With at Least One TEAE	xx (xx.x)
	xx (xx.x)
SOC1	xx (xx.x)
PT1	xx (xx.x)
PT2	xx (xx.x)

Table 9. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term by Period

Reporting data for a drug switch involves documenting relevant information to ensure clarity and transparency.

Include data on the safety and efficacy outcomes related to the switch:

Adverse Events: Document any adverse events experienced during or after the switch.

Therapeutic Response: Report on the clinical response to the new drug compared to the original drug.

CONCLUSION

This paper is primarily focusing on AESI, DLT and drug switch, which statistical programmers may encounter in early phase oncology trials. We present background information on the specific issues,

highlight the importance of these topics, and clarify the pain points posted on programming work. Hoping that would help statistical programmers figure out solutions when they deal with these kinds of challenges.

REFERENCES

1. “ICH Topic E2F Development Safety Update Report”, *EMEA/CHMP/ICH/309348/2008*, June 2008.

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-2-f-development-safety-update-report-step-3_en.pdf

2. “The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials: Report of CIOMS Working Group VII”, *Geneva 2006*.

https://cioms.ch/publications/product/development-safety-update-report-dsur-harmonizing-format-content-periodic-safety-report-clinical-trials-report-cioms-working-group-vii/

3. “ADaM Structure for Occurrence Data (OCCDS) Version 1.0”, *CDISC Analysis Data Model Team,* Feb 2016.

https://www.cdisc.org/system/files/members/standard/foundational/adam/ADaM_OCCDS_v1.0.pdf

4. Wong HH, Halford S. 2015. “Dose-limiting toxicity and maximum tolerated dose: still fit for purpose?”, Oct 2015 *The Lancet Oncology,*16:1287-1288

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CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Dandan Du
BeiGene (Beijing) Co., Ltd.
dandan.du@beigene.com