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Relative Dose Intensity in Oncology Trials: A Discussion of Two Approaches

Christiana Hawn and Dhruv Bansal, Catalyst Flex

ABSTRACT

This paper will explore the unique challenges of calculating relative dose intensity in early-phase oncology studies. Relative dose intensity, defined as the actual dose received divided by the prescribed dose according to the protocol, is an important endpoint in clinical trials. This is a straightforward calculation for drugs with daily pill administration, however it becomes more complicated when dealing with intravenous (IV) drugs on varying dosing schedules and cycle lengths as is common in early-phase oncology studies. This paper will present a mock scenario representing a typical early phase oncology study with multiple schedules and explore two different methods of calculating relative dose intensity. The first approach counts the number of expected doses based on the number of cycles completed compared to the number of doses received. This is a straightforward calculation and easy to interpret but does not account for time factors such as dosing delays and skipped cycles. The second approach incorporates the expected number of doses based on the duration of treatment compared to the actual number of doses received in that amount of time. We will demonstrate that the resulting dose intensity values between the two approaches can vary significantly. We will include examples for ADaM specifications and programming in SAS® and discuss the reasons to consider each approach.

INTRODUCTION

Dose intensity is calculated by taking the actual dose taken divided by the duration of treatment. A measure of protocol specified prescribed dose intensity can be determined using the dose expected per protocol for the same duration of treatment. Relative dose intensity provides a comparison between the actual dose intensity and prescribed dose intensity (Yao et. al, 2016). This is useful for analyzing the impact of both dose level changes throughout the course of treatment and missed doses or delays on dosing on the treatment effect.

In the context of a trial where the study drug is administered as pill with a fixed daily dose, the calculation of relative dose intensity is easily determined. Let's consider for example a hypothetical trial where the study drug is administered as a 100 mg pill taken twice a day for 10 days, and Subject A missed one day and therefore only took 18 of the 20 expected pills. The relative dose intensity for Subject A is calculated as follows:

Protocol: 100 mg pill taken 2 times a day for 10 days

Protocol specified total dose: 100 mg x 2 pills/day x 10 days = 2000 mg

Protocol-specified dose intensity: 2000 mg / 10 days = 200 mg/day

But the subject skipped a day and therefore only took 18 of the 20 pills….

Actual total dose: 1800 mg

Actual dose intensity: 180 mg/day

Relative dose intensity: 180 / 200 = 90%

The typical dosing schedules common in oncology trials present unique challenges in the calculation of relative dose intensity. Treatment is often defined in multiple week cycles, with infusions occurring on specified days within each cycle (ex. 28-day cycles with infusions on Day 1,8, and 15; 21-day cycles with infusions on Day 1,2, and 3). Treatment continues until disease progression, so subjects will be on the trial treatment for varying lengths of time. Since the prescribed dose is not equal over time (as in the above pill example) and does not have a protocol-defined duration, additional consideration must then be given to the duration of treatment used in the calculation of dose intensity. For example, simply using the date of last dose of treatment for the end of the duration does not account for the remainder of the dosing

interval in which the treatment ended. The assumptions made in dose intensity calculations for these types of trials need to be understood and defined, to understand what is being captured in the measure used.

The following is a discussion of two possible approaches for calculating relative dose intensity. Using an example data set, we will show the calculations for each method and the corresponding results. An examination of the differences provides insight into the considerations for choosing each method depending upon the intent of the analysis.

For the examples in this paper, we use a dosing schedule with 21-day cycles where the study drug is administered on Days 1, 2, and 3 of each cycle. The protocol specified dose is the same at each infusion, and the protocol specified dose level does not change throughout a subject's time on trial, although the prescribed dose could be reduced to an adverse event.

METHOD 1: PRESCRIBED VS ADMINISTERED DOSE

In this method, relative dose intensity is determined by considering the total dose specified per protocol considering each scheduled infusion day compared to the total dose received. Total dose specified per protocol is calculated by determining the number of days the subject was expected to receive treatment and multiplying by the starting dose level. Total dose received is the sum of the actual dose given at each of the scheduled infusion days (with skipped doses assigned a value of zero).

Figures 1-3 below display exposure data from the example ADEX data set for three subjects who each completed three cycles of treatment. Parameter Code = "PERFDOSE" indicates the actual dose received at the given visit, and Analysis Value is the dose received for each visit (with the value at Cycle 1 Day 1 reflecting the protocol specified dose level for the subject).

Using Subject A003 as an example, with a protocol specified starting dose of 46 mg, the relative dose intensity would be calculated as follows:

Protocol: 46 mg on Days 1, 2, and 3 of each 21-day cycle

Total planned dose: 46 x 9 days (3 cycles x 3 days) = 414 mg

But the subject had a dose reduction to 33 mg due to adverse event at Cycle 2 Day 1…

Total administered dose: 46 x 3 days (Cycle 1) + 33 x 6 days (Cycles 2 and 3) = 336 mg

Relative dose intensity: 320 / 342 = 81.2%

Figures 1-3 below display exposure data from the example ADEX data set for three subjects who each completed three cycles of treatment. Parameter Code = "PERFDOSE" indicates the actual dose received at the given visit, and Analysis Value is the dose received for each visit (with the value at Cycle 1 Day 1 reflecting the protocol specified dose level for the subject).

	Subject Identifier for the Study	Parameter Code	Analysis Visit	Analysis Visit (N)	Analysis Start Day	Analysis Value	Treatment Start Date	Analysis Start Date
1	A001	PERFDOS	Cycle 1 Day 1	101	1	44	07APR2020	07APR2020
2	A001	PERFDOS	Cycle 1 Day 2	102	2	44	07APR2020	08APR2020
3	A001	PERFDOS	Cycle 1 Day 3	103	3	44	07APR2020	09APR2020
4	A001	PERFDOS	Cycle 2 Day 1	201	22	44	07APR2020	28APR2020
5	A001	PERFDOS	Cycle 2 Day 2	202	23	44	07APR2020	29APR2020
6	A001	PERFDOS	Cycle 2 Day 3	203	24	44	07APR2020	30APR2020
7	A001	PERFDOS	Cycle 3 Day 1	301	45	44	07APR2020	21MAY2020
8	A001	PERFDOS	Cycle 3 Day 2	302	46	44	07APR2020	22MAY2020
9	A001	PERFDOS	Cycle 3 Day 3	303	47	44	07APR2020	23MAY2020

Figure 1: Exposure Data for Example Subject A001

	Subject Identifier for the Study	Parameter Code	Analysis Visit	Analysis Visit (N)	Analysis Start Day	Analysis Value	Treatment Start Date	Analysis Start Date
19	A002	PERFDOS	Cycle 1 Day 1	101	1	49	09SEP2020	09SEP2020
20	A002	PERFDOS	Cycle 1 Day 2	102	2	49	09SEP2020	10SEP2020
21	A002	PERFDOS	Cycle 1 Day 3	103	3	49	09SEP2020	11SEP2020
22	A002	PERFDOS	Cycle 2 Day 1	201	36	49	09SEP2020	14OCT2020
23	A002	PERFDOS	Cycle 2 Day 3	203	38	49	09SEP2020	16OCT2020
24	A002	PERFDOS	Cycle 3 Day 1	301	67	49	09SEP2020	14NOV2020
25	A002	PERFDOS	Cycle 3 Day 2	302	68	49	09SEP2020	15NOV2020
26	A002	PERFDOS	Cycle 3 Day 3	303	69	49	09SEP2020	16NOV2020

Figure 2: Exposure Data for Example Subject A002

	SUBJID	PARAMCD	AVISIT	AVISITN	ASTDY	AVAL	TRTSDT	ASTDT
35	A003	PERFDOS	Cycle 1 Day 1	101	1	46	06OCT2020	06OCT2020
36	A003	PERFDOS	Cycle 1 Day 2	102	2	46	06OCT2020	07OCT2020
37	A003	PERFDOS	Cycle 1 Day 3	103	3	46	06OCT2020	08OCT2020
38	A003	PERFDOS	Cycle 2 Day 1	201	29	33	06OCT2020	03NOV2020
39	A003	PERFDOS	Cycle 2 Day 2	202	30	33	06OCT2020	04NOV2020
40	A003	PERFDOS	Cycle 2 Day 3	203	31	33	06OCT2020	05NOV2020
41	A003	PERFDOS	Cycle 3 Day 1	301	57	33	06OCT2020	01DEC2020
42	A003	PERFDOS	Cycle 3 Day 2	302	58	33	06OCT2020	02DEC2020
43	A003	PERFDOS	Cycle 3 Day 3	303	59	33	06OCT2020	03DEC2020

Figure 3: Exposure Data for Example Subject A003

Figure 4 presents the value-level metadata (VLM) for the ADEX parameters used to calculate relative dose intensity using this first method.

Dataset	Variable	SASFieldName	Label	Type	Length	Origin	Method
ADEX	AVAL	PLNDOS	Planned Dose (mg)	integer	8	Derived	Set to EC.ECDOSE where ECMOOD='SCHEDULED'
ADEX	AVAL	ACTDOS	Actual Dose (mg)	integer	8	Derived	Set to EC.ECDOSE where ECMOOD='PERFORMED'
ADEX	AVAL	TOTDOS	Total Administered Dose (mg)	integer	8	Derived	Sum of all EC.ECDOSE where ECMOOD='PERFORMED'
ADEX	AVAL	TOTPLAN	Total Planned Dose (mg)	integer	8	Derived	Sum of all EC.ECDOSE where ECMOOD='SCHEDULED'
ADEX	AVAL	RELINT	Relative Dose Intensity (%)	integer	8	Derived	TOTDOS / TOTPLAN*100 Round to 1 decimal place.

Figure 4: VLM for Method 1 ADEX parameters

Table 1 displays the results for relative dose intensity using Method 1. Subject A001 received the protocol specified dose for all protocol specified infusions up until their end of treatment, resulting in a relative dose intensity of 100%. Subject A002 has a smaller relative dose intensity of 88.9% because they did not receive a Cycle 2 Day 2 infusion. Subject A003 has relative dose intensity of 81.2% due to a dose reduction (46 mg to 33 mg) at Cycle 2 Day 1 even though subject took dose at each planned cycle days.

Subject	Total Administered Dose (mg)	Total Planned Dose (mg)	Relative Dose Intensity (%)
A001	396	396	100
A002	392	441	88.9
A003	336	414	81.2

Table 1: Relative Dose Intensity Using Method 1

METHOD 2: DOSE OVER DURATION OF TREATMENT

In addition to the amount of dose received, this method accounts for the duration of treatment compared to the duration expected according to the protocol. The actual treatment duration is calculated until the end of the cycle in which the subject receives their last dose. Actual dose per cycle is compared to planned dose per cycle to determine relative dose intensity.

Considering Subject A003 again, relative dose intensity would be calculated as follows:

Protocol: 46 mg on Days 1, 2, and 3 of each 21-day cycle

Planned Dose Per Cycle: 46 mg/day x 3 days / cycle = 138 mg / cycle

But the subject had a dose reduction to 46 mg due to adverse event at Cycle 2 Day 1 and a seven-day delay prior to the start of both Cycle 1 and Cycle 2, for a total of 14 days of dose delays…

Total Administered Dose: 46 x 3 days (Cycle 1) + 33 x 6 days (Cycles 2 and 3) = 336 mg

Actual Treatment Duration: (21 days x 3 cycles + 14 days delayed) / 7 = 11 weeks

Actual Dose Per Cycle: 336 mg / (11 weeks / 3 weeks / cycle) = 91.64 mg / cycle

Relative Dose Intensity: 91.64 / 138 = 66.4%

Figure 5 presents VLM for the calculation of relative dose intensity using this method in ADEX.

Dataset	Variable	SASFIeldName	Label	Type	Length	Origin	Method
ADEX	AVAL	ACTWKS	Actual Treatment Duration (Weeks)	integer	8	Derived	Let Cx= final cycle in which subject received treatment ACTWKS=[(Date of CxD1 + 20) - TRTSDT + 1] / 7
ADEX	AVAL	ACTINT	Actual Dose (per cycle)	integer	8	Derived	ACTINT=TOTDOSE/(ACTWKS/3)
ADEX	AVAL	PLANINT	Planned Dose (per cycle)	integer	8	Derived	Let x=PLNDOS when VISIT=Cycle 1 Day 1 PLANINT=3x
ADEX	AVAL	RELINT	Relative Dose Intensity	integer	8	Derived	ACTINT/PLANINT*100 Round to 1 decimal place.

Figure 5: VLM for Method 2 ADEX parameters

Table 2 displays the results for relative dose intensity using Method 2. While Subject A001 had 100% relative dose intensity using Method 1, their relative dose intensity drops to 96.8% when calculated using Method 2 because of delays in starting Cycle 2 and 3. Similar results are observed for Subjects A002 and A003, with the impact of cycle delays evident in the lower relative dose intensities (64.5% and 66.4%, respectively, compared to 88.9% and 81.2% using Method 1).

Subject	Planned Dose Per Cycle (mg)	Actual Treatment Duration (weeks)	Actual Dose Per Cycle (mg)	Relative Dose Intensity (%)
A001	132	9.3	127.74	96.8
A002	147	12.4	94.84	64.5
A003	138	11	91.64	66.4

Table 2: Relative Dose Intensity Using Method 2

CONCLUSION

There are many factors to consider when evaluating relative dose intensity in oncology trials with infusion cycles. As illustrated by the two examples discussed in this paper, it is important to understand the purpose of the analysis and consider the implications of the assumptions inherent in the method chosen when calculating relative dose intensity.

REFERENCES

Yao B, Ye Y, Yu H. Data and analysis considerations in oncology clinical trials. *Biom Biostat Int J.* 2016; 4 (4): 136-142.

CONTACT INFORMATION

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

Christiana Hawn
Catalyst Flex
E-mail: christiana.hawn@catalystcr.com

Dhruv Bansal
Catalyst Flex
E-mail: dhruv.bansal@catalystcr.com