PharmaSUG 2025 - Paper DS-109

Impact of Drug Accountability on Drug Compliance and Dose Intensity in Clinical Trials

Vishal Gandhi, Milan Adesara, Merck & Co., Inc., Rahway, NJ, USA

ABSTRACT

In clinical trials involving oral drug administration with varying dosing frequencies, drug accountability is critical for assessing drug exposure, compliance, and treatment efficacy. Patients are typically dispensed a specific quantity of medication, with any unused tablets returned at subsequent visits. The returned medication is analyzed to determine key parameters, including the *Actual Consumed Dose, Actual Dose Intensity and Relative Dose Intensity*. These parameters provide a comprehensive understanding of patient adherence to the prescribed regimen, enabling the identification of potential deviations that may impact pharmacokinetic and study outcomes.

Ensuring accurate measurement of Drug Compliance directly influences the reliability of study results. Evaluating Actual Dose Intensity and Relative Dose Intensity allows reviewers to compare the administered dose with the intended dose and assess the degree to which patients adhere to the treatment plan. This information is essential for determining the effectiveness of the drug's efficacy and safety in real-world conditions. Thus, drug accountability serves as a cornerstone for the successful execution and interpretation of clinical trials.

This presentation will thoroughly explore various scenarios we faced while creating ADEXSUM dataset. By addressing this complexity, we aim to improve comprehension and outline a logical approach for deriving these parameters.

INTRODUCTION

In clinical trials involving oral drug administration, particularly those with varying dosing frequencies, drug accountability is a critical factor that influences the assessment of drug exposure, patient compliance, and treatment efficacy. Monitoring the quantity of medication dispensed to patients—and subsequently returned—provides invaluable data for evaluating adherence to the prescribed treatment regimen. This process involves analyzing the returned medication to calculate key parameters such as *Actual Consumed Dose*, *Actual Dose Intensity*, and *Relative Dose Intensity*.

These metrics are essential for a comprehensive understanding of patient adherence and drug utilization, enabling researchers to identify deviations that may impact pharmacokinetic outcomes and the overall interpretations of study results. Accurate measurement of drug compliance not only enhances the reliability of clinical trial findings but also informs the evaluation of a drug's efficacy and safety in real-world scenarios.

This paper aims to address the complexities encountered during the creation of the ADaM dataset, an initiative designed to refine the methodologies for deriving these essential parameters. By exploring various scenarios and challenges faced in this endeavor, we aim to enhance the comprehension of drug accountability and its significance in the successful execution and interpretation of clinical trials.

DRUG COMPLIANCE

Drug compliance is crucial in clinical trials as it directly impacts the validity and reliability of results, ensuring that the observed outcomes accurately reflect the drug's efficacy and safety. High compliance rates allow for a more accurate assessment of treatment effects and facilitate effective safety monitoring by accurately linking adverse events to the medication. Regulatory agencies also prioritize compliance data during the

drug approval process, and fostering adherence promotes greater patient engagement and education about their treatment.

Drug Compliance is defined as the percentage of doses a study participant has taken (*Actual Consumed Dose*) compared to the total number of doses prescribed in the Protocol.

$$\text{Drug Compliance} = \frac{\text{Actual Consumed Dose}}{\text{Prescribed Total Dose}} * 100$$

Dose Compliance is explained using below example of study participant A001-101.

	STUDYID	USUBJID	ECTRT	ECDOSE	ECDOSU	ECMOOD	ECDOSRGM	ECDOSFRQ	ECADJ	VISIT	ECSTDTC	ECENDTC
1	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		C1D1	01JAN2024	28JAN2024
2	A001	A001-101	TRT001	20	mg	Performed	3 Weeks on, 1 Week off	BID		C1D1	01JAN2024	28JAN2024
3	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		C2D1	29JAN2024	25FEB2024
4	A001	A001-101	TRT001	20	mg	Performed	3 Weeks on, 1 Week off	BID		C2D1	29JAN2024	25FEB2024
5	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		C3D1	26FEB2024	24MAR2024
6	A001	A001-101	TRT001	20	mg	Performed	3 Weeks on, 1 Week off	BID		C3D1	26FEB2024	24MAR2024
7	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		C4D1	25MAR2024	21APR2024
8	A001	A001-101	TRT001	20	mg	Performed	3 Weeks on, 1 Week off	BID		C4D1	25MAR2024	21APR2024
9	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		C5D1	22APR2024	19MAY2024
10	A001	A001-101	TRT001	0	mg	Performed	3 Weeks on, 1 Week off	BID	Adverse Event	C5D1	22APR2024	19MAY2024
11	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		C6D1	20MAY2024	29MAY2024
12	A001	A001-101	TRT001	20	mg	Performed	3 Weeks on, 1 Week off	BID		C6D1	20MAY2024	29MAY2024
13	A001	A001-101	TRT001	20	mg	Scheduled	3 Weeks on, 1 Week off	BID		EOT	29MAY2024	29MAY2024
14	A001	A001-101	TRT001	20	mg	Performed	3 Weeks on, 1 Week off	BID		EOT	29MAY2024	29MAY2024

Figure 1: Exposure data of Patient A001-101

	STUDYID	USUBJID	DATESTCD	DATEST	DAORRES	DAORRESU	DADTC	VISIT
1	A001	A001-101	DISPAMT	Dispensed Amount	50	Capsule	01JAN2024	C1D1
2	A001	A001-101	DISPAMT	Dispensed Amount	50	Capsule	29JAN2024	C2D1
3	A001	A001-101	RETAMT	Returned Amount	8	Capsule	29JAN2024	C2D1
4	A001	A001-101	DISPAMT	Dispensed Amount	50	Capsule	26FEB2024	C3D1
5	A001	A001-101	RETAMT	Returned Amount	10	Capsule	26FEB2024	C3D1
6	A001	A001-101	DISPAMT	Dispensed Amount	50	Capsule	25MAR2024	C4D1
7	A001	A001-101	RETAMT	Returned Amount	8	Capsule	25MAR2024	C4D1
8	A001	A001-101	DISPAMT	Dispensed Amount	0	Capsule	22APR2024	C5D1
9	A001	A001-101	RETAMT	Returned Amount	16	Capsule	22APR2024	C5D1
10	A001	A001-101	DISPAMT	Dispensed Amount	50	Capsule	20MAY2024	C6D1
11	A001	A001-101	RETAMT	Returned Amount	0	Capsule	20MAY2024	C6D1
12	A001	A001-101	DISPAMT	Dispensed Amount	0	Capsule	29MAY2024	EOT
13	A001	A001-101	RETAMT	Returned Amount	34	Capsule	29MAY2024	EOT

Figure 2: Drug Accountability data of Patient A001-101

Study Identifier	Unique Subject Identifier	Actual Consume Dose (mg)	Prescribed Total Dose (mg)	Drug Compliance (%)
A001	A001-101	3480	5000	69.60

Table 1: *Drug Compliance* of Patient A001-101

ACTUAL CONSUMED DOSE

The Pill Count method is the most employed approach for calculating the *Actual Consumed Dose*. This method involves researchers counting the number of pills that are dispensed to and returned by participants to assess the percentage of medication consumed during a clinical trial. Drug accountability data plays a crucial role in ensuring accurate documentation of drug administration throughout the treatment process.

Referring to the examples provided in Figures 1 and 2, patient A001-101 is scheduled to take a daily dose of 40 mg for a total of 21 days within each treatment cycle (EC.ECDOSRGMN = '3 Weeks on,1 Week off').

At the first visit (C1D1), the patient was dispensed a total of 50 capsules, each containing 20 mg of the investigational drug. Following this, at the subsequent visit, the patient returned 8 capsules. This indicates that the patient consumed a total of 42 capsules, which corresponds to a daily intake of 2 capsules per day, aligning with the prescribed dosing regimen.

In contrast, during the second visit (C2D1), the patient was again dispensed 50 capsules. Upon the patient's return visit, only 10 capsules were returned. This suggests that the patient consumed 40 capsules instead of the expected 42, indicating a discrepancy in the number of doses taken. This difference can be attributed to the fact that the patient missed one day dose (40 mg) during the second treatment cycle, as evidenced by the returned capsule count.

This data underscores the importance of precise tracking of drug consumption, as even minor discrepancies in dose intake can have an impact on treatment outcomes and patient safety. It also highlights the role of drug accountability data in identifying and rectifying dosing inconsistencies, ensuring that the patient adheres as closely as possible to the prescribed regimen.

```
/* Actual Consumed Dose */

proc sql;
  create table da_acd as
    select a.studyid, a.usubjid, a.disp_ds - b.retn_ds as acd /* Dispensed dose - Returned dose*/
      from
        (select p.studyid, p.usubjid,
                sum(p.daorres * q.ecdose) as disp_ds /* SUM of total dispensed dose */
           from da (where = (datestcd = "DISPAMT")) as p
             left join                          /* Merge DA & EC to get the total dispensed dose */
                ec (where = (ecmood = "Scheduled")) as q
              on p.usubjid = q.usubjid and
                 p.dadtc = q.ecstdtc
              group by p.studyid, p.usubjid) as a
         left join
        (select x.studyid, x.usubjid,
                sum(x.daorres * y.ecdose) as retn_ds /* SUM of total returned dose */
           from da (where = (datestcd = "RETAMT")) as x
             left join                          /* Merge DA & EC to get the total returned dose */
               ec (where = (ecmood = "Scheduled")) as y
             on x.usubjid = y.usubjid and
                x.dadtc = y.ecstdtc
              group by x.studyid, x.usubjid) as b
           on a.studyid = b.studyid and
              a.usubjid = b.usubjid
            order by a.studyid, a.usubjid;
quit;
```

Program 1: Determine *Actual Consumed Dose*

PRESCRIBED TOTAL DOSE

The *Prescribed Total Dose* refers to the comprehensive quantity of medication that is intended to be administered to a patient over a designated treatment period, as outlined in the clinical trial protocol.

```
/* Prescribed Total Dose */

proc sql;
   create table ec_acd as
      select studyid, usubjid, sum(ecdose * 2) as acd /* ECDOSFRQ = "BID" */
            from ec
                  where ecmood = "Scheduled"
                        group by studyid, usubjid;
quit;
```

Program 2: Determine *Prescribed Total Dose*

ACTUAL DOSE INTENSITY

This parameter is crucial in clinical trials, as it can significantly influence both the efficacy and tolerability of treatments. Understanding actual dose intensity is essential for evaluating the overall impact of a treatment in a clinical trial setting.

Actual Dose Intensity (ADI) is defined as the amount of total drug delivered to the patient during treatment duration.

$$\text{Actual Dose Intensity} = \frac{\text{Actual Consumed Dose}^{a}}{\text{Prescribed Treatment Duration}^{b}}$$

[a] *Actual Consume Dose is determine in Drug Compliance section.*

[b] *Number of days the study participants consumed the study drug medication.*

Study Identifier	Unique Subject Identifier	Actual Consume Dose (mg)	Prescribed Total Dose (mg)	Drug Compliance (%)	Prescribed Treatment Duration (Days)	Actual Dose Intensity (mg/day)
A001	A001-101	3480	5000	69.60	113	30.93

Table 2: *Actual Dose Intensity* for Patient A001-101

PRESCRIBED TREATMENT DURATION

The evaluation of *Prescribed Treatment Duration* is influenced by several complicating factors, including variations in dosing regimens and interruptions in drug administration.

Dose Regimen Variability: When participants are randomized to different dosing regimens, it is essential to exclude the days they were not receiving medication from the total treatment duration.

For instance, as illustrated in Figure 1, Patient A001-101 is assigned to a dosing regimen where the patient receives the study drug for 3 weeks, followed by a 1-week break from administration.

Drug Interruption Events: Additionally, any days during which the study drug is temporarily paused for safety concerns or other clinical reasons must also be subtracted from the overall treatment duration.

In the example provided in Figure 1, the patient experiences a dose interruption due to an Adverse Event.

```
/* Step 1: Separate the DISPENSED and RETURNED */

data dispense return;
   set da;
   if datestcd = 'DISPAMT' then output dispense;
      else if datestcd = 'RETAMT' then output return;
run;


/* Step 2: Calculate the dispensed total dose, total dispensed pill, total returned dose & total
returned pills */

proc sql;
  create table dispense1 as
    select usubjid, visit, dadtc, sum(totdose) as disp_totdose, sum(daorres) as disp_pill
      from dispense
        group by usubjid, dadtc, visit
          order by usubjid, dadtc, visit;
  create table return1 as
    select usubjid, visit, dadtc, sum(totdose) as retn_totdose, sum(daorres) as ret_pill
      from return
        group by usubjid, dadtc, visit
          order by usubjid, dadtc, visit;
quit;


/* Step 3: Merge Dispensed Dose with Return Dose */

data dispretn;
  merge return1 dispense1;
  by usubjid dadtc visit;
  disp_visit = lag(visit);
  disp_dose = lag(disp_totdose);
  disp_dtc = lag(input(dadtc, yymmdd10.));
  format disp_dtc date9.;
run;


/* Step 4: Calculate the Prescribed number of days */

data dispretn_l;
  set dispretn;

/* Calculation of cycle days between the returned date and dispensed date */
  if not missing(dadtc) and not missing(disp_dtc) then cydy = input(dadtc, yymmdd10.)- disp_dtc ;

/* Calculation of month value on the basis of cycle days */
  if not missing(cydy) then cymon = cydy/28;

/* If the number of cycle days > 21 (3Wkon1Wkoff regimen) then calculating the prescribed days on
pro-rata basis of the month and week (7 days)*/
  if not missing(cydy) and not missing(cymon) and cydy > 21 then p_day = (cydy - (cymon * 7));

/* If the number of cycle days <= 21 then prescribed days is assigned as cycle days*/
  if not missing(cydy) and not missing(cymon) and cydy <= 21 then p_day = cydy;
run;
```

Program 3: Determine the *Prescribed Treatment Duration*

RELATIVE DOSE INTENSITY

Relative Dose Intensity (RDI) is a critical parameter in clinical trials, as it provides valuable insights into both the effectiveness of the treatment being studied and the safety of the patients involved. By quantifying the actual dose received by participants relative to the planned dose, RDI serves as an essential metric for assessing treatment efficacy, and overall therapeutic outcomes.

Monitoring RDI is paramount for several reasons. First, it ensures that study participants are receiving an adequate dose of the investigational therapy, which is crucial for achieving the desired therapeutic effect. Inadequate dosing can lead to suboptimal outcomes, undermining the primary objectives of the trial.

Second, RDI plays a vital role in patient safety. By tracking RDI, clinicians can quickly identify trends where dose reductions or treatment interruptions occur due to adverse events. This information enables timely interventions, such as dose adjustments or supportive care measures, to mitigate risks while still delivering effective treatment.

- An RDI of 100% indicates that the study participants have received the full planned dose.
- An RDI of less than 100% indicates a reduction in the intensity of the treatment, which may occur due to adverse effects, toxicity, patient non-compliance, or other clinical considerations.
- An RDI of more than 100% is typically uncommon and may suggest that the patient received doses higher than planned, potentially due to adjustments in treatment.

Relative Dose Intensity (RDI) is defined as the ratio of *Actual Dose Intensity* to the *Prescribed Dose Intensity* by the study participants during specific treatment duration.

$$\text{Relative Dose Intensity} = \frac{\text{Actual Dose Intensity}}{\text{Prescribed Dose Intensity}^{a}} * 100$$

[a] *Prescribed Dose Intensity is defined as the ratio of Prescribed Dose Consumed to Prescribed Treatment Duration. It is important to note that all considerations previously outlined in the Actual Dose Intensity section will also apply while calculating Prescribed Dose Intensity*

Study Identifier	Unique Subject Identifier	Actual Consume Dose (mg)	Prescribed Total Dose (mg)	Drug Compliance (%)	Prescribed Treatment Duration (Days)	Actual Dose Intensity (mg/day)	Prescribed Dose Intensity (mg/day)	Relative Dose Intensity (%)
A001	A001-101	3480	5000	69.60	113	30.93	44.44	69.59

Table 3: *Relative Dose Intensity* for Patient A001-101

CONCLUSION

We continue to emphasize that *Drug Compliance*, *Actual Dose Intensity (ADI)*, and *Relative Dose Intensity (RDI)* are essential components in assessing treatment exposure and patient adherence in clinical study analyses. The content we have shared in this paper aims to assist users in effectively calculating these metrics to support robust and consistent reporting. Before implementing any provided frameworks, we recommend that users conduct thorough validation, regulatory compliance, and high-quality deliverables. While the outlined steps cover the foundational processes for calculating *Drug Compliance*, *ADI*, and *RDI*, we recognize that specific implementation may vary depending on study design and therapeutic area. We trust that this guidance will prove to be a valuable resource for incorporating these critical exposure metrics into clinical data analysis and reporting.

REFERENCES

SAS Institute Inc. (2016). SAS® 9.4 Graph Template Language: User's Guide, Fifth Edition. Cary, NC: SAS Institute Inc. Retrieved from https://documentation.sas.com/api/docsets/grstatug/9.4/content/grstatug.pdf?locale=en

D L Longo, P L Duffey, V T DeVita Jr, M N Wesley, S M Hubbard, and R C Young; *"The calculation of actual or received dose intensity: a comparison of published methods."* https://ascopubs.org/doi/10.1200/JCO.1991.9.11.2042

Karen Y Wonders, Kathryn Schmitz, Jay Harness; *"Dose Delays, Dose Reductions, and Relative Total Dose Intensity in Patients With Advanced Cancer Who Exercised During Neoadjuvant Chemotherapy Treatment"* https://pmc.ncbi.nlm.nih.gov/articles/PMC10126785/

Pol Boudes MD a; *"Drug Compliance in Therapeutic Trials: A Review"* https://www.sciencedirect.com/science/article/pii/S0197245698000051#BIB1

SR Warren 1, DW Raisch, HM Campbell, PD Guarino, JS Kaufman, E Petrokaitis, DS Goldfarb, JM Gaziano, RL Jamison; *"Medication adherence assessment in a clinical trial with centralized follow-up and direct-to-patient drug shipments."* https://pmc.ncbi.nlm.nih.gov/articles/PMC6178218/#R1

Lars Osterberg, M.D., and Terrence Blaschke, M.D.; *"Adherence to Medication "* https://www.nejm.org/doi/full/10.1056/NEJMra050100

ACKNOWLEDGMENTS

The authors would like to thank subject matter experts from the BARDS TA standard management teams from Merck & Co., Inc., Rahway, NJ, USA, for their advice and guidance on this paper/presentation. The authors are also grateful for reviewing the paper and providing feedback by Erica Davis, Shi Changhong, Abhilash Vasu Chimbirithy, Jing Su, Sandeep Meesala, and our department head Amy Gillespie.

CONTACT INFORMATION

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

Vishal Gandhi
Merck & Co., Inc., Rahway, NJ, USA
vishal.gandhi@merck.com

Milan Adesara
Merck & Co., Inc., Rahway, NJ, USA
milan.adesara@merck.com

TRADEMARK