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A Navigation to the Drug-Drug Interaction (DDI) Study: Implementation Frameworks, Carry-over effects and Advanced Statistical Approaches

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ABSTRACT

DDI in vivo is a situation in which one drug modifies the pharmacological effect of another drug when both are administered together, leading to reduced therapeutic efficacy or unexpected side effects. Anticancer drugs are highly prone to DDIs due to its common inhibition of some enzymes and drug transporters. As a result, the DDI study in oncological trial is often designed to investigate the impact of single- and multiple doses (steady state) of study treatment on the PK of probe drugs. In some DDI studies, carry-over effects occur when a drug persists into the subsequent treatment period, influencing the analysis results and biasing pharmacokinetic data. This paper outlines the overall DDI study design, carry-over criteria and their impacts on programming work frames such as implementation of data mapping and statistical methodologies, considering multiple drugs and different administration periods. Challenges of SAS programs for statistical modeling in pharmacokinetic parameters are included as well.

INTRODUCTION

DDI studies are specific clinical pharmacology investigations designed to determine if and how one drug affects the pharmacokinetics, pharmacodynamics, safety or efficacy of another drug when both are administered together. Given TKI (Tyrosine kinase inhibitor)'s complex metabolism, transporter interactions, narrow therapeutic index, and common concomitant medications in cancer treatment, understanding and mitigating DDIs is paramount for optimizing TKI efficacy and ensuring patient safety. Clinical DDI studies yield the critical data to predict, avoid, and manage these potentially dangerous interactions, ultimately maximizing the therapeutic benefit of these powerful targeted agents.

This paper focus on complex study designs, pharmacokinetic sampling strategies for multiple drugs, including probe substrates and treatment drug, DDI endpoints as well as carry-over effects criteria and sensitivity analysis.

Corresponding SDTM/ADaM domains need to be designed based on analyses needs, and for DDI study, how to map PK parameters data to PC/PP and ADPC/ADPP were challenging.

The primary concern in SDTM (PC/PP) mapping happens when structurally accommodating carry-over adjusted values, while preserving traceability to original measurements and complying with CDISC standards at the same time.

ADaM (ADPC/ADPP) datasets implementation requires detailed derivation rules to manage analysis flags that define distinct analysis sets, such as primary analysis or sensitivity analysis, and makes the generation of related TLGs smoothly.

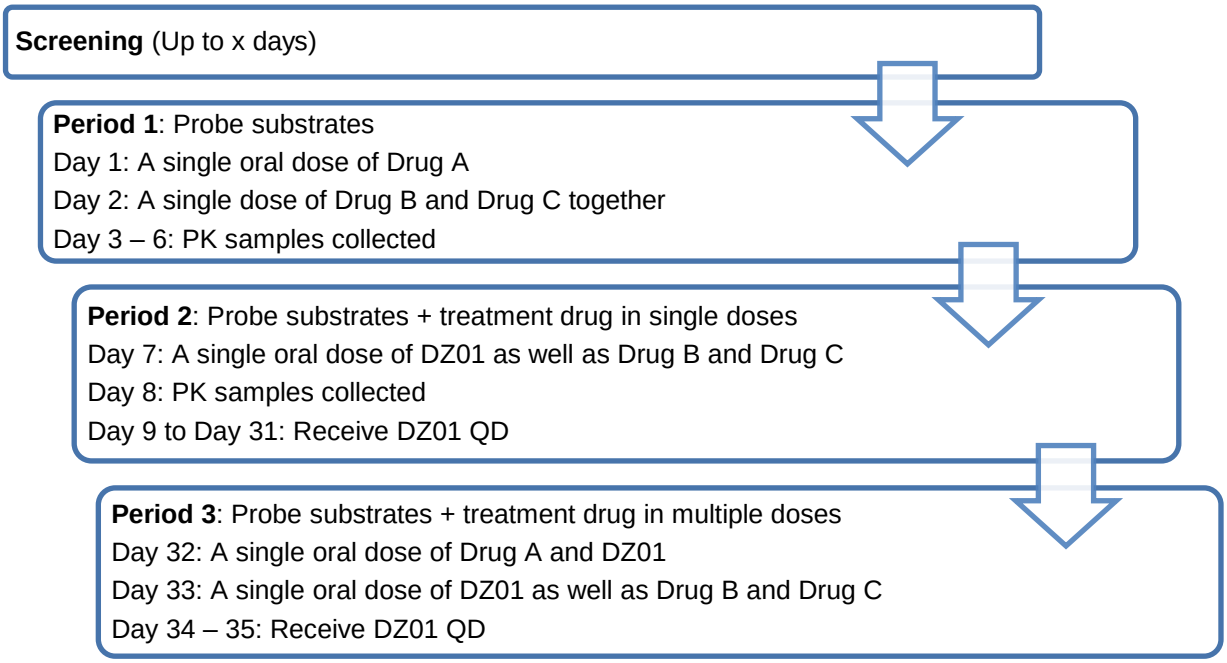
Due to the requirement of statistical assessment on pharmacokinetic parameters, programmers may meet the challenge of seeking the computational approaches to build Wilcoxon Signed rank distribution based on recursive formula for the cumulative distribution function. The stepwise algorithms and examples of code are systematically presented in this paper.

DDI STUDY DESIGN

Depending on the fundamental of DDI study, which aims to comparing two conditions (1. Probe substrate alone 2. Probe substrate + interacting drug), subjects in a DDI study always take the probe substrate alone in the first treatment period and then take probe substrates and treatment drug together in the subsequent period. These two phases are connected via a sufficient washout period to dissipate the previous treatment and isolate the effects. If a steady state is necessary, then another period is expected, following an adequate pre-administration of treatment drug to make sure that greatest invocation on enzyme or transporters would be reached.

To better understand the conceptual background from data collection to key analyses, a Phase 1, open-label, non-randomized oncological study is shown as an example below. This study assesses the effect of treatment drug (DZ01) on the pharmacokinetics of cocktail probes following single and/or multiple oral dosing of treatment drug (DZ01) in the fed condition. The population of this DDI study should be patients with cancer since this population has a good tolerance to the treatment drug based on clinical safety data. The cocktail probes include three representative substrates for CYP3A4, P-gp, (BCRP and OATP1B1), and they are named after Drug A, Drug B and Drug C.

STUDY FLOW CHART:



PK SAMPLING SCHEDULE

The concentrations of DZ01 (and its metabolite), drug A (and its metabolite), drug B, drug C in plasma will be collect. Depending on the study flow, corresponding pk sampling and administration schedule is shown as below:

Day	**Time points (hours)**	**Blood sampling (√) & administration (x) for DZ01**		**Blood sampling (√) & administration (x) for Drug B/C**		**Blood sampling (√) & administration (x) for Drug A**	
Day 1	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12					√	x
Day 2	24 for Drug A Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12			√	x	√	
Day 3	24			√			
Day 4	48			√			
Day 5	72			√			
Day 6	96			√			

Day	Time points (hours)	Blood sampling (√) & administration (x) for DZ01		Blood sampling (√) & administration (x) for Drug B/C		Blood sampling (√) & administration (x) for Drug A	
Day 7	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	√ (Pre-dose, 6)	x	√	x		
Day 8	24			√			
Day 9	48		x	√			
Day 10 - 17			x				
Day 18 ± 1	Pre-dose	√	x				
Day 19 - 24			x				
Day 25 ± 1	Pre-dose	√	x				
Day 26 - 31			x				
Day 32 ± 1	Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12		x			√	x
Day 33 ± 1	24 for A Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	√ (Pre-dose, 6)	x	√	x	√	
Day 34 ± 1	24	√	x	√			
Day 35 ± 1	48	√	x	√			

Table 1. pk sampling and administration schedule

Day 3 to Day 6 is the washout period to link period 1 and period 2. The 23-day pretreatment period (Days 9 to Day 31) before probe drug administration ensures steady-state modulation of relevant enzymes/transporters by the treatment drug.

ENDPOINTS

Endpoints for DDI studies focus on PK alternations, PD effects, safety and qualify exposure changes. As a result, common endpoints are plasma concentrations of probe substrates and derived PK parameter, such as C_{max}, measuring the highest concentration in blood and AUC_{0-t}, which is the Area Under the Curve, measuring total drug exposure over time. Since this study involves not only single dose but also multiple doses of treatment study, the ratio of AUC and the associated 90% CIs are also primary DDI endpoints.

CARRY-OVER EFFECT

Carryover effects refer to the persistent influence of a treatment administered in the previous period on the outcomes measured in the subsequent one. The effects can compromise study validity by distorting treatment comparisons, introducing bias and violating the assumption of period independence.

Although a washout period is designed to avoid carry-over effects, sometimes it is inevitable when some participants meet the carry-over criteria in cross-over study:

Period 2 (Day 7) pre-dose concentration >5% of C_{max} for Drug B or Drug C

Once the carry-over effect is detected, adjustments on the concentrations and other PK parameters will be calculated. The adjustments would no doubt influence data handling in the production of SDTM and ADaM, and a sensitivity statistical analysis will be performed if appropriate. Implementations will be discussed in corresponding parts below.

PROGRAMMING WORKFLOW

ACRF

Figure 1 shows separate pages designed for probe substrates and treatment drugs respectively. The main difference is the fixed planned timepoints. Since the plasma collection is provided by central lab with external data, only basic information such as linking ID and sampling date/timepoints are collected in EDC.

Figure 2 shows related pages for pk sampling, since the administration schedule is complicated and four drugs are planned to take, each visit where patients take any drug, the dosing date and time would be collected. This page is essential for subsequent mapping since Date/Time of the reference point (dose administration) must be captured and associated with every individual record.

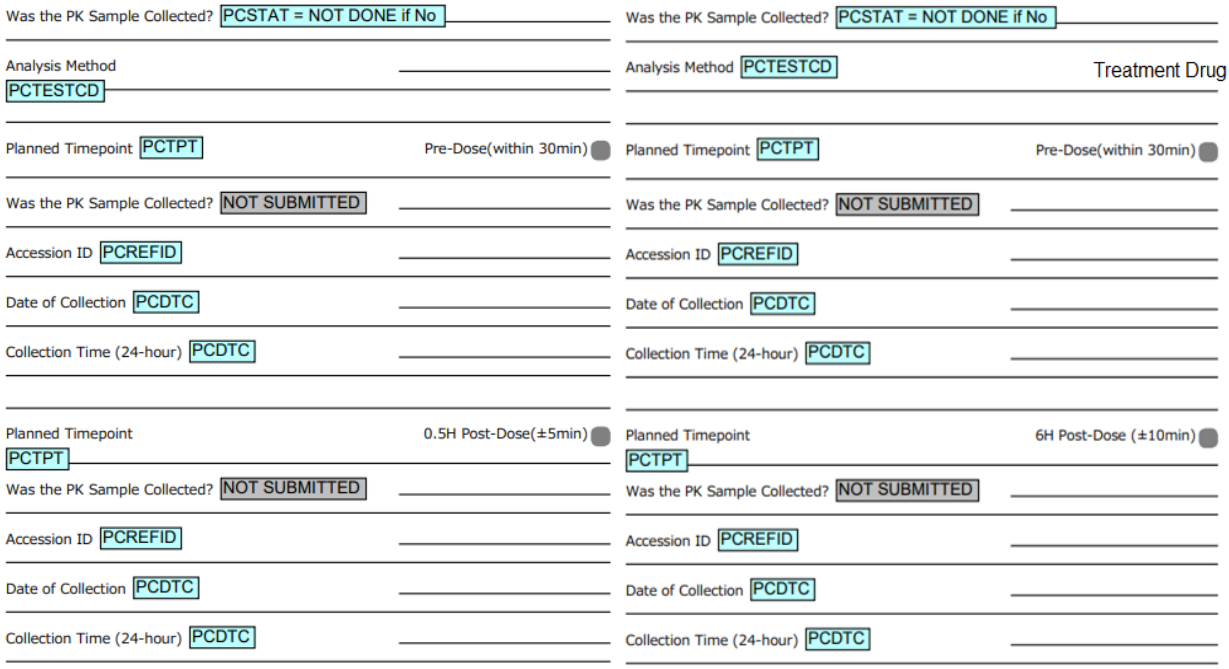


Figure 1. aCRF for probe substrates and treatment drugs

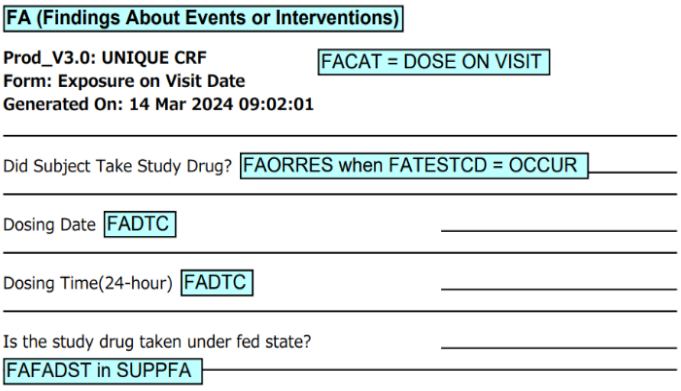


Figure 2. aCRF for exposure on visit date

SDTM

When producing SDTM domains (PC and PP), the key difference from regular derivations lies in the mapping of carry-over adjustments and our objective is to identify approaches for inputting the values. At first, we tried to add PCSCAT= “CARRYOVER” to distinguish the original pk parameters and the adjusted ones. However, this would trigger a pinnacle 21 issue (SD1117: Duplicate records), which is “The

structure of Findings class domains should be one record per Finding Result per subject. No Finding Result with the same Test Short Name (--TESTCD) and the same Qualifier variables at the same timepoint for the same Subject (USUBJID) are expected". Obviously, the original one and adjusted one share a same timepoint. As an alternative method, a supp variable would be introduced to address the issue. However, this approach was immediately dismissed because carry-over effects are crucial in the following analysis and retaining these values in the main dataset is much more efficient compared to extracting them from SUPPPC/SUPPPP when developing ADaM datasets. Based on the two key considerations discussed earlier, one way to store the adjusted values is to introduce new --TESTCDs. We append "C" to the –TESTCD variable suffix (e.g., CMAXC) and assign "Carry Over" as the corresponding –TEST value (e.g., Max Conc Carry Over) to identify these special cases. This naming convention can not only increase coding efficiency but also maintain consistency in ADaM datasets.

ADAM

For this study, pharmacokinetics Analysis Set (PKS) is all dosed patients who had at least one quantifiable plasma concentration collected post-dose with no important protocol deviations or Adverse Events that may impact the analysis of the PK data and PKS is the foundation for all subsequent data handling.

Core steps for ADPC development include manipulating variables such as timing variables (deriving ADTM and calculating ADY), parameter variables standardization (mapping SDTM --TESTCD to ADaM PARAMCD/ PARAM), analysis value variables (AVAL/AVALC/AVALU) and adding analysis flags. ANL01FL eligible for primary analysis population mainly based on exclusion status and PK sampling time window validity which is defined in SAP.

As for ADPP, one noteworthy aspect is the analysis flags. In this study, three analyses flags (ANLxxFL) were created to represent three different selections of analyses records.

Variable	Label	Programming Notes
ANL01FL	Analysis Flag 01	Considering exclude flag: AE/CM/PK analysis exclude flag and Carry-over effect, reflect by PP.PPEXCL
ANL02FL	Analysis Flag 02	Primary analysis flag, exclude the carry over effect population
ANL03FL	Analysis Flag 03	Sensitivity analysis: 1) include the carryover effect population and replace the original data with the adjusted one (ending with C) 2) For drug A, include those were excluded due to CM in primary analysis

Table 2. Analysis flags and derivation rules

ANL01FL is a straightforward flag derived exclusively from PP.PPEXCL (Exclude Flag), and "Y" of PPEXCL indicates the record should be excluded from this analysis set. For ANL02FL, based on ANL01FL, we choose subjects whose PPCOEFL (Carry-Over Effect Flag: original records before adjustments) not equal to "Y" and exclude all PARAMCDs ending with "C". For ANL03FL, the derivation requires substrate-dependent rules, because carry-over effects are only anticipated for Drug B/C and sensitivity analysis for Drug A obeys another rule. While the protocol-defined threshold for carry-over effects is greater than 5%, we adjusted all records with detectable pre-dose concentrations to maximize sensitivity analysis robustness. These records are not flagged with either Carry-Over Effect Flag or Exclude Flag. So, for Drug B/C the first step is to identify all subjects with concentration adjustments on Day 7 and exclude all these selected records when getting ANL03FL. Next, for Drug A, if PPEXCLCM (CM Exclude Flag) = 'Y' then adds ANL03FL = 'Y', and all other Drug A records inherits ANL02FL='Y' status.

Generally, TRTA is used in TFLs for different treatment groups. However, TRTA in ADPC/ADPP represents the actual treatments for different periods and "Probe Drugs Only" and "Probe Drugs + DZ01 x mg" are used, so specified probe drugs cannot be selected. As a result, to enhance the table generation efficiency, ATRTDSC (Analysis Treatment Regimens Description) is introduced to both ADPC and ADPP, and table 3 is part of the structure of ADPP:

SUBJ ID	AVISIT	PARAMCD	PARAM	ATRTDSC	COEFL	ANL01FL	ANL02FL	ANL03FL
001	Day 2	CMAX	Max Conc (ng/mL)	DrugB	N	Y	Y	Y
001	Day 7	AUC0_48	AUC from 0 to 48 (h*ng/mL)	DrugB + DZ01 Single Dose	N	Y	Y	
001	Day 7	AUC0_48C	AUC from 0 to 48 Carry Over (h*ng/mL)	DrugB + DZ01 Single Dose	N	Y		Y
001	Day 33	TMAX	Time of CMAX (h)	DrugB + DZ01 Multiple Dose	N	Y	Y	Y
007	Day 2	AUC0_48	AUC from 0 to 48 (h*ng/mL)	DrugB	Y	Y	Y	Y
007	Day 7	AUC0_48	AUC from 0 to 48 (h*ng/mL)	DrugB + DZ01 Single Dose	Y			
007	Day 7	AUC0_48C	AUC from 0 to 48 Carry Over (h*ng/mL)	DrugB + DZ01 Single Dose	Y	Y		Y

Table 3. Structure of ADPP

STATISTICAL METHODS AND PROGRAMMING CHALLENGES

MIXED MODEL

For probe substrates, natural log-transformed AUC (and/or $AUC_{0\text{-}t}$) and C_{max} will be compared across treatments using a mixed-effects model with treatments as fixed effect and patient as random effect. Proc mixed is used to establish the mixed model and 90% CIs of the GLS mean ratios for AUCs.

Example Code:

```
ods output Estimates = estimate;
proc mixed data= __input_dataset;
   by paramn param;
   class usubjid atrtdsc;
   model aval = atrtdsc/ddfm = kr;
   random usubjid;
   estimate 'DrugA' intercept 1 atrtdsc 1 0 /e cl alpha = 0.1;
   estimate 'DrugA + DZ01 Multiple Dose' intercept 1 atrtdsc 0 1 /e cl
alpha = 0.1;
   estimate 'DrugA + DZ01 Multiple Dose versus DrugA' atrtdsc -1 1 /e cl
alpha = 0.1;
run;
ods output close;
```

E requests that the **L** matrix coefficients be displayed. The ODS name of this "L Matrix Coefficients" table is "Coef." And CL requests that t-type confidence limits be constructed.

Least square means for each treatment difference with 90% CI between each treatment were estimated and back transformed as the GLS means and ratios in original scale.

Figure 3 is the final output of this statistical assessment.

Parameter Treatment	n	GLS Mean	Ratio of GLS Mean (versus Drug A)	90% CI of the Ratio
$AUC_{0\text{-}inf}$ (ng*h/mL)				
Drug A	x	x		
Drug A + DZ01 Multiple Dose	x	x	x	(x, x)
$AUC_{0\text{-}t}$ (ng*h/mL)				
Drug A	x	x		
Drug A + DZ01 Multiple Dose	x	x	x	(x, x)
C_{max} (ng/mL)				
Drug A	x	x		
Drug A + DZ01 Multiple Dose	x	x	x	(x, x)

Figure 3. Statistical Assessment of Effect of Multiple Dose DZ01 on Pharmacokinetic Parameters of Drug A - Primary Analysis

WILCOXON SIGNED RANK TEST

In the statistical assessment of effect of single dose (Treatment Drug) on Tmax of Drug A/B/C, Hodges-Lehmann estimation provided median differences and 90% confidence intervals, while the Wilcoxon signed-rank test generated associated p-values for paired observations.

A notable implementation challenge arises in SAS: Construction of the Wilcoxon signed-rank distribution is required to obtain Hodges-Lehmann median differences with corresponding 90% CIs. This computational approach included 6 steps.

1. Calculate the difference (diff) between AVALs of probe substrate and probe substrate + DZ01 Multiple Dose. Either zero difference or missing values are excluded.
2. Count the number of difference (n).
3. Get Walsh Averages for diff (Given a dataset of n numbers (X_1, X_2, ... X_n), a Walsh average is calculated as $(X_i + X_j) / 2$, where i and j range from 1 to n and $i \leq j$)
4. Utilize recursive algorithm for Wilcoxon signed rank distribution: $P_n(T) = [P_{n-1}(T) + P_{n-1}(T - n)] / 2$, where T is the sum of positive ranks, $P_{n-1}(T)$ is probability when new observation is negative, and $P_{n-1}(T - n)$ is probability when new observation is positive.
5. Determine the critical value k for constructing a Hodges-Lehmann confidence interval associated with the Wilcoxon signed-rank test according to α. (conf = 1 - 2 * CDF)
6. The Confidence Interval now can be constructed using the Walsh averages: [(k+1)-th smallest Walsh average, (M - k)-th smallest Walsh average], m = n * (n+1) / 2 and m can be verified because m should be the number of Walsh averages.

The SAS code for step 4, which is the construction of Wilcoxon signed rank distribution, is shown below:

```
%macro wilcoxon_signedrank_dist(n=);
 /*------------------------------------------------------------
  Macro: wilcoxon_signedrank_dist
  Purpose: Build Wilcoxon signed-rank distribution for sample size n
  Parameters: n = number of observations
  Output Dataset: wilcoxon_dist (variables: T, prob, cum_prob)
  ------------------------------------------------------------*/

    /* Validate input */
    %if %sysevalf(&n < 1) %then %do;
        %put ERROR: n must be >= 1;
        %return;
    %end;
```

```
    /* Initialize base distribution (n=1) */
    data dist;
        T = 0; prob = 0.5; output;
        T = 1; prob = 0.5; output;
    run;

    /* Recursively build distribution */
    %do i = 2 %to &n;
        /* Create new possible T values */
        data new_dist;
            set dist;
            /* Case 1: Negative sign - keep original T */
            output;
            /* Case 2: Positive sign - add current rank (i) */
            T = T + &i;
            output;
        run;

        /* Aggregate probabilities */
        proc summary data=new_dist nway;
            class T;
            var prob;
            output out=dist(drop=_type_ _freq_) sum=;
        run;

        /* Scale probabilities */
        data dist;
            set dist;
            prob = prob / 2;  /* Account for binary choice */
        run;
    %end;

    /* Finalize distribution */
    data wilcoxon_dist;
        set dist;
        /* Calculate cumulative probability */
        retain cum_prob 0;
        prob = round(prob, 1e-10);
        cum_prob + prob;

        m = &n*(&n+1)/2; /* m is the max of T */
        keep T prob cum_prob m;
    run;

    proc sort data=wilcoxon_dist;
        by T;
    run;

    /* Delete intermediate datasets */
    proc datasets library=work nolist;
        delete dist new_dist;
    quit;

%mend;
```

```
%wilcoxon_signedrank_dist(n=5);
```

Wilcoxon Signed-Rank Distribution (n=5)

T	PROB	CUM_PROB
0	0.031250	0.031250
1	0.031250	0.062500
2	0.031250	0.093750
3	0.062500	0.156250
4	0.062500	0.218750
5	0.093750	0.312500
6	0.093750	0.406250
7	0.093750	0.500000
8	0.093750	0.593750
9	0.093750	0.687500
10	0.093750	0.781250
11	0.062500	0.843750
12	0.062500	0.906250
13	0.031250	0.937500
14	0.031250	0.968750
15	0.031250	1.000000

Figure 4. Wilcoxon Signed-Rank Distribution when n=5

Fortunately, p-value with Wilcoxon signed rank test can be calculated directly using proc univariate.

Example code:

```
ods select TestsForLocation;
ods output TestsForLocation=wilcoxon;
proc univariate data=cleaned cipctldf(alpha=0.10) mu0=0;
   var diff;
run;
ods output close;
```

CONCLUSION

Due to complex multi-drug regimens and carry-over effects, data management in drug-drug interaction (DDI) studies requires fundamentally different approaches than standard clinical trials. This necessitates flexible modifications to pharmacokinetic (PK) and pharmacodynamic (PD) related datasets to ensure analytical validity.

For SDTM mapping, the fundamental consideration is to avoid triggering Pinnacle 21 issues. The challenge is to appropriately store carry-over adjusted values and make production of ADaM less complicated. Our solution is creating --TESTCD/--TEST and append “C/ “Carry over” to the original ones, which not only complying with CDISC standards but also enhance the efficiency of developing ADPC/ADPP.

For ADaM development, programmers should mainly pay attention to the logic of analysis flags. For ADPC, derivation rules for analysis flags are straightforward and need to take time window defined in SAP into consideration. While in ADPP, two points make the development of ANLxxFL variables demands rigorous attention. Th first one comes to distinct criteria held by the primary and sensitivity analysis and the other one is that the inclusion or exclusion rules is drug-specified.

Finally, the statistical assessment in DDI studies need to calculate median difference and corresponding Confidence Intervals depending on the paired values. The programming challenge is that programmers need to construct the Wilcoxon Signed-Rank distribution in SAS based on recursive algorithm and understand the statistics such as Walsh Averages.

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