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A Methodology of Laboratory Data Reporting of Potentially Clinical Significant Abnormality (PCSA) for Clinical Study Report

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ABSTRACT

In February 2005, the Center for Drug Evaluation and Research (CDER) issued a Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review [1], which points out that reporting of Potentially Clinically Significant Abnormalities (PCSA) from laboratory, Vital signs, and ECG values for selected parameters is critical to clinical safety review. This paper describes a methodology, which shows step-by-step process to build a standard library for PCS criteria dataset for selected serum chemistry parameters and hematology parameters, and automatically generate CDISC-compliant standard variables in ADLB for PCS criteria, and create SAS® table programming templates for PCSA tables and their listing. The standardization of PCS criteria dataset facilitates generating of CDISC-compliant standard variables in ADLB for PCS criteria and PCSA table template. With this strategy, the standard SAS programs for both ADaM datasets and PCSA tables can be easily developed across the studies. Technical accuracy and operational efficiency can be ensured.

INTRODUCTION

In FDA submission, safety and tolerability of the study drug will usually be assessed throughout the study based on AEs, vital signs, laboratory test results (chemistry, hematology, and urinalysis), and ECG results. The Center for Drug Evaluation and Research (CDER) considered a clinical safety review “should focus on patients whose laboratory values deviate substantially from the reference range” in a Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review [1], since the changes in laboratory values are “much more likely to identify significant problems than mean or median change from baseline”. Reports of Potentially Clinically Significant Abnormalities (PCSA) from laboratory, Vital signs, and ECG values for selected parameters are important parts of the safety review as they provide patient information of significant deviation from normal while on treatment by treatment groups.

A sample PCSA table was provided in Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review as below, which compared the incidence of Potentially Clinically Significant Changes in any of selected serum chemistry parameters across the treatment groups.

Table 7.1.7.3.2.1
Incidence of Potentially Clinically Significant Changes in Serum Chemistry Parameters
for Pool of Placebo Controlled Studies for New Drug
Cutoff Date

Serum Chemistry Parameters and PCS Criteria L=Low; H=High; ULN=Upper Limits of Normal	**Treatment Groups**								
	New Drug			**Placebo**			**Active Control**		
	Total	**Abnormal**		**Total**	**Abnormal**		**Total**	**Abnormal**	
	Pts	**Nbr**	**%**	**Pts**	**Nbr**	**%**	**Pts**	**Nbr**	**%**
Albumin-L (< 2.5 g/dl)									
Alkaline P’tase-H (> 400 U/L)									
Bilirubin, total-H (> 2 mg/dl)									
BUN-H (> 30 mg/dl)									
CK-H (> 3XULN)									
Calcium-L (< 7 mg/dl)									
Calcium-H (> 12 mg/dl)									
…									
Uric Acid (F)-H (> 8.0 mg/dl)									
Uric Acid (M)-H (> 10.0 mg/dl)									

Table 1. A Sample PCSA Table

In the above table, PCS criteria include PCS-Low criteria, e.g., Albumin-L (<2.5g/dl) and PCS-High criteria, e.g., Bilirubin, total-H (> 2 mg/dl). The denominator for calculating the incidence is the number of subjects with non-PCS baseline and at least one post-baseline assessment. A separate listing should provide patient identification for those patients meeting the criterion.

Decisions about criteria for identifying outliers should, if possible, be made at the pre-NDA meeting, and the PCS criteria will be defined in SAP with the input from Medical Directors, as shown in Appendix 1.

Usually PCS criteria could be classified into 5 categories shown in the table 2.

Category	PCS-Low Criteria	PCS-High Criteria
Only One Criterion Defined by One Lab Value	Albumin <2.5 g/dL	Bilirubin, Total >=2.0 mg/dL
Two Criteria defined by Lab Value and Gender	Hemoglobin <=9.5 g/dL (Female) Hemoglobin <=11.5 g/dL (Male)	Triglycerides >=120 mg/dL (Female) Triglycerides >=160 mg/dL (Male)
More than one Criterion in Same Direction		exp. 1: Alanine Aminotransferase (U/L) >=3 x ULN Alanine Aminotransferase (U/L) >=5 x ULN exp. 2: Urate >9 mg/dL Urate >8 mg/dL (Female) Urate >10 mg/dL (Male)
Same Lab Parameter with both PCS-Low and PCS-High Criteria	Calcium <7 mg/dL	Calcium >12 mg/dL
Criteria defined by Lab Value, Change from Baseline, and Gender	Hematocrit <=32% and 3 point decrease from baseline (Female) Hematocrit <=37% and 3 point decrease from baseline (Male)	

Table 2. Classification of PCS Criteria

PCS Criteria are provided by the company clinical group and documented in Statistical Analysis Plan (SAP). An example of Laboratory PCS criteria are shown in appendix 1. The corresponding table shell for a chemistry PCSA table is shown in appendix 2. Variables for generating PCSA tables in ADaM ADLB will be created based on SAP. In ADLB, two or three analysis criterion variables, CRIT1, CRIT2, and /or CRIT3 along with criterion evaluation result flags, CRIT1FL,CRIT2FL, and/or CRIT3FL are applied to identify whether a PCS criterion is met for selected parameters.

However, the programming for Laboratory PCS criteria is very labor-intensive as there are a large amount of laboratory parameters with PCSA analysis. Also there could be some changes in laboratory parameters collected in different studies, which adds more complexity to PCSA programming. The variation of criteria among different therapeutic areas makes it error-prone for ADaM/TFL programming, and even harder to standardize SAS code to develop ADLB for PCS criteria and PCSA tables.

Another challenging part of Laboratory PCS programming occurs when there are missing categories in PCSA tables, which is not uncommon in the clinical trial as PCS criteria are related to extreme changes in laboratory values. A PCS Criteria Template in a table programming will be needed to incorporate all missing categories. It is tedious and likely to make mistakes to manually prepare the PCS templates.

In this paper, we propose a methodology to build a standard library of PCS criteria for selected serum chemistry parameters and hematology parameters, which makes it possible to automatically generate CDISC-compliant standard variables in ADLB for PCS criteria, and create PCS Criteria Templates for PCSA tables and their listing. This strategy is to standardize SAS programs for both PCS variables in ADLB and PCSA tables across the studies, and avoids the tedious manual work with effectiveness and efficiency.

DEVELOP PCSA-RELATED VARIABLES IN ADLB FOR PCSA TABLES

PCS VARIABLES CRIT1, CRIT1FL, CRIT2, CRIT2FL, CRIT3, AND CRIT3FL

In ADaM IG 1.1, there are two BDS Standard Variables CRITy (Analysis Criterion y) and CRITyFL (Criterion y Evaluation Result Flag) to identify whether a PCS criterion is met for a parameter. Per the Classification of PCS criterion in Table 2, CRIT1 and CRT1FL are applied to PCS-Low, and CRIT2 and CRT2FL along with CRIT3 and CRT3FL are for PCS-High. When developing a SAS program for PCSA tables, we can select records with first non-missing minimal value among all post-baseline visits for all CRIT1 criteria, and select records with first non-missing maximal value among all post-baseline visits for all CRIT2 criteria. If there are more than one criterion for PCS-High,

CRIT3 and CRIT3FL are applied for the second Criterion for PCS-High. The specifications for variables CRIT1, CRIT1FL, CRIT2, CRIT2FL, CRIT3, and CRIT3FL are shown in Appendix 3.

FLAG VARIABLES (ANL01FL AND ANL02FL) AND POPULATION VARIABLE (ITTR01FL, ITTR02FL, AND ITTR03FL) FOR ADLB

Variable ANLzzFL is to flag the "worst" value for each parameter among the post-baseline lab values in our standard ADLB programming. ANL01FL is use to select the first non-missing minimal value among all post-baseline visits, while ANL02FL is for the first non-missing maximal value, as defined in Appendix 3. ANL01FL and CRIT1FL are combined to select unique PCS-Low records for selected parameters, and ANL02FL and CRIT2FL are for unique PCS-High records. If there are more than one criterion for PCS-High, ANL03FL and CRIT3FL are for unique PCS-High records.

Variable ITTRzzFL in Appendix 3 identifies whether or not the parameter of a subject was in the PCSA analysis. ITTR01FL is to calculate the denominators of PCS-Low Criteria in PCSA tables, ITTR02FL the denominators of first PCS-High criteria. If there is more than one criterion of PCS-High, ITTR03FL is to calculate the denominators of second PCS-High criteria.

SUBJID	PARCAT1	PARAMCD	PARAM	LBORRESU	APHASE	AVISIT	AVAL	ANL01FL	ANL02FL	CRIT1	CRIT1FL	CRIT2	CRIT2FL	CRIT3	CRIT3FL	ITTR01FL	ITTR02FL	ITTR03FL
840226-502	CHEMISTRY	HDL	HDL Cholesterol (mg/dL)	mg/dL	PRE-TREATMENT	Baseline	29			HDL Cholesterol <=30 mg/dL	Y							
840226-502	CHEMISTRY	HDL	HDL Cholesterol (mg/dL)	mg/dL	FIRST TREATMENT	V3-Day 8	28	Y	Y	HDL Cholesterol <=30 mg/dL	Y							
840226-502	CHEMISTRY	HDL	HDL Cholesterol (mg/dL)	mg/dL	FIRST TREATMENT	V7-Day 36	28			HDL Cholesterol <=30 mg/dL	Y							
840104-509	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	PRE-TREATMENT	Baseline	290					Triglycerides >=120 mg/dL (Female)	Y					
840104-509	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	FIRST TREATMENT	V3-Day 8	377		Y			Triglycerides >=120 mg/dL (Female)	Y					
840104-509	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	FIRST TREATMENT	Early Termination Visit At Stage 1	292					Triglycerides >=120 mg/dL (Female)	Y					
840104-509	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	FOLLOW-UP	Follow-up Visit At Stage 1	264	Y				Triglycerides >=120 mg/dL (Female)	Y					
840226-502	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	PRE-TREATMENT	Baseline	146											
840226-502	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	FIRST TREATMENT	V3-Day 8	153	Y									Y	
840226-502	CHEMISTRY	TRIG	Triglycerides (mg/dL)	mg/dL	FIRST TREATMENT	V7-Day 36	170		Y			Triglycerides >=160 mg/dL (Male)	Y				Y	
840219-503	CHEMISTRY	URATE	Urate (mg/dL)	mg/dL	PRE-TREATMENT	Baseline	9.8					Urate >9 mg/dL	Y					
840219-503	CHEMISTRY	URATE	Urate (mg/dL)	mg/dL	FIRST TREATMENT	V3-Day 8	10.5		Y			Urate >9 mg/dL	Y	Urate >10 mg/dL (Male)	Y			Y
840219-503	CHEMISTRY	URATE	Urate (mg/dL)	mg/dL	FIRST TREATMENT	V7-Day 36	8.7	Y										Y

Display 1. An example of ADLB Data with PCS variables (CRIT1, CRIT1FL, CRIT2, CRIT2FL, CRIT3, CRIT3FL) and Flag variables (ANL01FL, ANL02FL, ITTR01FL, ITTR02FL, and ITTR03FL)

Note: ITTR02FL was NOT set to 'Y' for Urate of subject: 840219-503 above due to its PCS baseline for criterion: Urate >9 mg/dL, contrast to ITTR03FL.

GENERAL METHOD FOR GENERATING PCSA TABLES

GENERAL METHOD FOR GENERATING PCS VARIABLES CRIT1, CRIT1FL, CRIT2, CRIT2FL, CRIT3, AND CRIT3FL IN ADLB PROGRAMMING

Based on SAP and ADaM specifications for PCS Variables, ADaM programming source code for PCS variables CRIT1, CRIT1FL, CRIT2, CRIT2FL, CRIT3, and CRIT3FL are shown as below.

```
*** CRIT1, CRIT1FL ***;
if paramcd='ALB' & lborresu='g/dL' & .<aval<2.5 then do; crit1fl='Y'; crit1='Albumin <2.5 g/dL'; end;
if paramcd='BICARB' & lborresu='mmol/L' & .<aval<=18 then do; crit1fl='Y'; crit1='Bicarbonate <=18 mmol/L'; end;
if paramcd='CA' & lborresu='mg/dL' & .<aval<7 then do; crit1fl='Y'; crit1='Calcium <7 mg/dL'; end;
if paramcd='CL' & lborresu='mmol/L' & .<aval<=90 then do;crit1fl='Y'; crit1='Chloride <=90 mmol/L';end;
if paramcd='GLUC' & lborresu='mg/dL' & .<aval<50 then do; crit1fl='Y'; crit1='Glucose <50 mg/dL'; end;
if paramcd='HDL' & lborresu='mg/dL'   & .<aval<=30 then do; crit1fl = 'Y'; crit1 = 'HDL Cholesterol <=30 mg/dL'; end;
if paramcd='PHOS' & lborresu='mg/dL' & .<aval<2 then do; crit1fl='Y'; crit1='Phosphate <2 mg/dL'; end;
if paramcd='K' & lborresu='mmol/L' & .<aval<3 then do; crit1fl='Y'; crit1='Potassium <3 mmol/L'; end;
if paramcd='SODIUM' & lborresu='mmol/L' & .<aval<130 then do; crit1fl='Y'; crit1='Sodium <130 mmol/L'; end;
if paramcd='HCT' & lborresu='%' & .<aval<=32 & .<CHG<=-3 & sex='F' then do; crit1fl='Y'; crit1='Hematocrit <=32% and 3 point decrease
from baseline (Female)'; end;
if paramcd='HCT' & lborresu='%' & .<aval<=37 & .<CHG<=-3 & sex='M' then do; crit1fl='Y'; crit1='Hematocrit <=37% and 3 point decrease
from baseline (Male)'; end;
if paramcd='HGB' & lborresu='g/dL' & .<aval<=9.5 & sex='F' then do; crit1fl='Y'; crit1='Hemoglobin <=9.5 g/dL (Female)'; end;
if paramcd='HGB' & lborresu='g/dL' & .<aval<=11.5 & sex='M' then do; crit1fl='Y'; crit1='Hemoglobin <=11.5 g/dL (Male)'; end;
if paramcd='NEUT' & lborresu='10^3/uL' & .<aval<1.5 then do; crit1fl='Y'; crit1='Neutrophils, Absolute <1.5x10^3/uL'; end;
if paramcd='PLAT' & lborresu='10^3/uL' & .<aval<75.1 then do; crit1fl='Y'; crit1='Platelets <75.1x10^3/uL'; end;
if paramcd='WBC' & lborresu='10^3/uL' & .<aval<=2.8 then do; crit1fl='Y'; crit1='Leukocytes <=2.8x10^3/uL'; end;
*** CRIT2, CRIT2FL ***;
if paramcd='ALP' & lborresu='U/L' & aval>=3*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Alkaline Phosphatase (U/L) >=3 x ULN'; end;
if paramcd='ALT' & lborresu='U/L' & aval>=3*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Alanine Aminotransferase (U/L) >=3 x ULN'; end;
if paramcd='AST' & lborresu = 'U/L' & aval>=3*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Aspartate Aminotransferase (U/L) >=3 x ULN';
end;
if paramcd='BICARB' & lborresu='mmol/L' & aval>=30 then do; crit2fl='Y'; crit2='Bicarbonate >=30 mmol/L'; end;
if paramcd='BILI' & lborresu='mg/dL' & aval>=2 then do; crit2fl='Y'; crit2='Bilirubin, Total >=2.0 mg/dL'; end;
if paramcd='BUN' & lborresu='mg/dL' & aval>30 then do; crit2fl='Y'; crit2='Blood Urea Nitrogen >30 mg/dL'; end;
if paramcd='CA' & lborresu='mg/dL' & aval>12 then do; crit2fl='Y'; crit2='Calcium >12 mg/dL'; end;
if paramcd='CHOL' & lborresu='mg/dL' & aval>300 then do; crit2fl='Y'; crit2='Cholesterol, Total >300 mg/dL'; end;
if paramcd='CK' & lborresu='U/L' & aval>3*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Creatine Kinase (U/L) >3 x ULN'; end;
if paramcd='CL' & lborresu='mmol/L' & aval>=118 then do; crit1fl='Y'; crit1='Chloride >=118 mmol/L'; end;
if paramcd='CREA' & lborresu='mg/dL' & aval>=2 then do; crit2fl='Y'; crit2='Creatinine >=2.0 mg/dL'; end;
if paramcd='GGT' & lborresu='U/L' & aval>=3*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Gamma Glutamyl Transferase (U/L) >=3 x ULN';
end;
if paramcd='GLUC' & lborresu='mg/dL' & aval>200 then do; crit2fl='Y'; crit2='Glucose >200 mg/dL'; end;
if paramcd='LDH' & lborresu='U/L' & aval>3*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Lactate Dehydrogenase (U/L) >3 x ULN'; end;
if paramcd='LDL' & lborresu='mg/dL' & aval>=160 then do; crit2fl='Y'; crit2='LDL Cholesterol >=160 mg/dL'; end;
if paramcd='PHOS' & lborresu='mg/dL' & aval>5 then do; crit2fl='Y'; crit2='Phosphate >5 mg/dL'; end;
if paramcd='K' & lborresu='mmol/L' & aval>5.5 then do; crit2fl='Y'; crit2='Potassium >5.5 mmol/L'; end;
if paramcd='PROLCTN' & lborresu='ng/mL' & aval>1*anrhi & anrhi ne . then do; crit2fl='Y'; crit2='Prolactin (ng/mL) >1 x ULN'; end;
if paramcd='SODIUM' & lborresu='mmol/L' & aval>150 then do; crit2fl='Y'; crit2='Sodium >150 mmol/L'; end;
if paramcd='TRIG' & lborresu='mg/dL' & aval>=120 & sex='F' then do; crit2fl='Y'; crit2='Triglycerides >=120 mg/dL (Female)'; end;
if paramcd='TRIG' & lborresu='mg/dL' & aval>=160 & sex='M' then do; crit2fl='Y'; crit2='Triglycerides >=160 mg/dL (Male)'; end;
if paramcd='TSH' & lborresu='uIU/mL' & aval>5.5 then do; crit2fl='Y'; crit2='Thyrotropin >5.5 uIU/mL'; end;
if paramcd='URATE' & lborresu='mg/dL' & aval>9 then do; crit2fl='Y'; crit2='Urate >9 mg/dL'; end;
if paramcd='EOS' & lborresu='10^3/uL' & aval>1 then do; crit2fl='Y'; crit2='Eosinophils >1x10^3/uL'; end;
if paramcd='PLAT' & lborresu='10^3/uL' & aval>=700 then do; crit2fl='Y'; crit2='Platelets >=700x10^3/uL'; end;
if paramcd='WBC' & lborresu='10^3/uL' & aval>=16 then do; crit2fl='Y'; crit2='Leukocytes >=16x10^3/uL'; end;
*** CRIT3, CRIT3FL ***;
if paramcd='URATE' & lborresu='mg/dL' & aval>8 & sex='F' then do; crit3fl='Y'; crit3='Urate >8 mg/dL (Female)'; end;
if paramcd='URATE' & lborresu='mg/dL' & aval>10 & sex='M' then do; crit3fl='Y'; crit3='Urate >10 mg/dL (Male)'; end;
```

GENERAL METHOD FOR GENERATING PCSA TABLES

There are two types of PCSA Tables: PCSA Table by Post-Baseline Visits, and PCSA Table at Any Post-Baseline Visit. We use the second for the presentation in this paper. Two flags, ANL01FL and CRIT1FL, are used to select PCS-Low records at any post-baseline visit per selected parameter per subject, ANL02FL and CRIT2FL, ANL02FL and/or CRIT3FL are for PCS-High records. The PCSA table programming codes are shown as below.

```
Proc sort data = adam.adlb out =adlb;
    where saffl = 'Y' & parcat1 = 'CHEMISTRY' & aperiodc = 'STAGE 1' & basetype = 'Stage 1 Safety Period';
    by paramcd param trtan trta usubjid ;
 run;
*** get number of subjects who have PCS  ***;
proc freq data=adlb(where=(crit1fl = 'Y' and anl01fl = 'Y' and ittr01fl = 'Y')) noprint;
      table paramcd*param*crit1*trtan  / list missing out=pcs1(keep=paramcd param trtan count crit1);
run;
proc freq data=adlb(where=(crit2fl = 'Y' and anl02fl = 'Y' and ittr02fl = 'Y')) noprint;
      table paramcd*param*crit2*trtan  / list missing out=pcs2(keep=paramcd param trtan count crit2);
run;
proc freq data=adlb(where=(crit3fl = 'Y' and anl02fl = 'Y' and ittr03fl = 'Y')) noprint;
      table paramcd*param*crit3*trtan  / list missing out=pcs3(keep=paramcd param trtan count crit3);
run;
```

```
data allpcs1;
      set pcs1(in=a rename=(crit1=_crit)) pcs2(in=b rename=(crit2=_crit)) pcs3(in=c rename=(crit3=_crit));
     by paramcd param _crit trtan;
   length source $8;
   if a then source = 'CRIT1'; if b then source = 'CRIT2'; if c then source = 'CRIT3';
run;
proc sort data=allpcs1;by paramcd param _crit trtan;run;
proc transpose data=allpcs1 out=allpcs2 prefix=trt;
      where _crit > '';
      by paramcd param _crit source;
      id trtan;
     var count;
run;
data pcs;
      set allpcs2;
      by paramcd param _crit;
      if first.paramcd then do; _ord1 + 1; _ord2 = 1;end;
      else _ord2 + 1;
run;

*** get the denominator for PCS table  ***;
proc sort data = adlb(where=(ittr01fl='Y')) out = adlb1 nodupkey;by paramcd param trtan usubjid;run;
proc freq data=adlb1 noprint;
      table paramcd*param*trtan / list missing out=total1;
run;
proc transpose data=total1 out=total1(drop=_label_ _name_) prefix=tot1_;
      by paramcd param;
      var count;
      id trtan;
run;
proc sort data = adlb(where=(ittr02fl='Y')) out = adlb2 nodupkey;by paramcd param trtan usubjid;run;
proc freq data=adlb2 noprint;
      table paramcd*param*trtan / list missing out=total2;
run;
proc transpose data=total2 out=total2(drop=_label_ _name_) prefix=tot2_;
      by paramcd param;
      var count;
      id trtan;
run;
proc sort data = adlb(where=(ittr03fl='Y')) out = adlb3 nodupkey;by paramcd param trtan usubjid;run;
proc freq data=adlb3 noprint;
      table paramcd*param*trtan / list missing out=total3;
run;
proc transpose data=total3 out=total3(drop=_label_ _name_) prefix=tot3_;
      by paramcd param;
      var count;
      id trtan;
run;

data final1; *** Generate Final Dataset for PCSA Table Output ***;
      merge pcs(in=a) total1 total2 total3;
      by paramcd param;
      if a;
      length _npct1-_npct3 $40.;
      array col[3] _npct1-_npct3;
      array count[3] trt1-trt3;
      array tot[3] tot1-tot3;
      array tot1_[3] tot1_1-tot1_3;
      array tot2_[3] tot2_1-tot2_3;
      array tot3_[3] tot3_1-tot3_3;
      do i = 1 to 3;
          if source = 'CRIT1' then tot[i]=tot1_[i];
          if source = 'CRIT2' then tot[i]=tot2_[i];
          if source = 'CRIT3' then tot[i]=tot3_[i];
          if count[i] in (., 0) then count[i] = 0;
          if tot[i] in (., 0) then tot[i] = 0;
          if count[i] = 0 then col[i] = '  0/' || put(tot[i], 3.);
          else col[i] = put(count[i], 3.0) || '/' || put(tot[i], 3.) || ' (' || put(100*count[i]/tot[i], 5.1) || ')';
       end;
       keep  _ord1 _ord2 _crit source _npct1-_npct3 paramcd;
run;
proc sort data=final1; by _ord1 _ord2; run;
```

The final dataset ready for PCSA table output can be shown in Display 2. The data only contains non-missing categories for PCS criteria.

_ORD1	_ORD2	_CRIT	PARAMCD	SOURCE	_npct1	_npct2	_npct3
1	1	Cholesterol, Total >300 mg/dL	CHOL	CRIT2	2/96 (2.1)	0/18	1/20 (5.0)
2	1	Creatine Kinase (U/L) >3 x ULN	CK	CRIT2	1/95 (1.1)	1/18 (5.6)	1/20 (5.0)
3	1	Glucose >200 mg/dL	GLUC	CRIT2	1/96 (1.0)	0/18	0/20
4	1	HDL Cholesterol <=30 mg/dL	HDL	CRIT1	1/96 (1.0)	0/16	0/19
5	1	Potassium >5.5 mmol/L	K	CRIT2	3/97 (3.1)	0/18	0/20
6	1	LDL Cholesterol >=160 mg/dL	LDL	CRIT2	6/80 (7.5)	1/17 (5.9)	1/16 (6.3)
7	1	Phosphate >5 mg/dL	PHOS	CRIT2	0/96	1/18 (5.6)	0/20
8	1	Prolactin (ng/mL) >1 x ULN	PROLCTN	CRIT2	1/92 (1.1)	0/16	0/19
9	1	Triglycerides >=120 mg/dL (Female)	TRIG	CRIT2	14/54 (25.9)	2/12 (16.7)	1/12 (8.3)
9	2	Triglycerides >=160 mg/dL (Male)	TRIG	CRIT2	3/54 (5.6)	2/12 (16.7)	1/12 (8.3)
10	1	Urate >10 mg/dL (Male)	URATE	**CRIT3**	1/97 (1.0)	0/18	0/20

Display 2. An Example of Final Dataset (final1) for PCSA Table Output with Only Non-Missing PCS criteria

If there are only few laboratory parameters which satisfy the PCS criteria, most of the PCSA categories will not be shown in the table, which is similar to Lab normal shift table An example of a PCSA table with only non-missing PCS criteria is shown in Display 3. However all parameters in PCS criteria should be presented in PCSA tables.

Company Name Page 1 of 1
Study No. XXX-yyy

Table 14.3.4.3.1
Number (Percentage) of Subjects with Potentially Clinically Significant (PCS) Values in Chemistry at Any Post-Baseline Visit during Stage 1 Safety Period
- Entire Safety Population

	Stage 1 Treatment Group		
Parameter / PCS Criteria	Treatment A (N=97) n/m (%)	Treatment B (N=21) n/m (%)	Treatment C (N=21) n/m (%)
Cholesterol, Total >300 mg/dL	2/96 (2.1)	0/18	1/20 (5.0)
Creatine Kinase (U/L) >3 x ULN	1/95 (1.1)	1/18 (5.6)	1/20 (5.0)
Glucose >200 mg/dL	1/96 (1.0)	0/21	0/21
HDL Cholesterol <=30 mg/dL	1/96 (1.0)	0/18	0/20
LDL Cholesterol >=160 mg/dL	6/80 (7.5)	1/17 (5.9)	1/16 (6.3)
Phosphate >5 mg/dL	0/96	1/18 (5.6)	0/20
Potassium >5.5 mmol/L	3/97 (3.1)	0/18	0/20
Prolactin (ng/mL) >1 x ULN	1/92 (1.1)	0/16	0/19
Triglycerides >=120 mg/dL (Female)	14/54 (25.9)	2/12 (16.7)	1/12 (8.3)
Triglycerides >=160 mg/dL (Male)	3/54 (5.6)	2/12 (16.7)	1/12 (8.3)
Urate >10 mg/dL (Male)	1/97 (1.0)	0/18	0/20

n is the number of subjects who met the PCS criteria. m is the number of subjects with non-PCS baseline and at least one post-baseline assessment
Source Data: Listing 16.2.8.1.2

Display 3. An Example of PCSA Table with Only Non-Missing PCS criteria

GENERAL METHOD FOR CREATING PCS CRITERIA TEMPLATES FOR PCSA TABLE

In order to include the complete set of PCSA categories in a PCSA table, a template shown in Display 4, has to be generated for all defined PCS criteria so that the dataset for PCSA table outputting contains all PCSA categories in the template as Display 5. In the final data for PCSA table output, variable **SOURCE** provides the source of the PCS criteria. The value could be CRIT1, CRIT2, and/or CRIT3. If variable **SOURCE** is missing, the PCSA records come

from the PCS Criteria Template. In Display 5, only PCS criterion for total cholesterol comes from ADLB variable CRIT2. All other criteria come from the template.

_ORD1	_ORD2	_ROWTEXT	_CRIT	PARAM
1	1	Albumin <2.5 g/dL	Albumin <2.5 g/dL	Albumin (g/dL)
2	1	Alkaline Phosphatase (U/L) >=3 x ULN	Alkaline Phosphatase (U/L) >=3 x ULN	Alkaline Phosphatase (U/L)
3	1	Alanine Aminotransferase (U/L) >=3 x ULN	Alanine Aminotransferase (U/L) >=3 x ULN	Alanine Aminotransferase (U/L)
4	1	Aspartate Aminotransferase (U/L) >=3 x ULN	Aspartate Aminotransferase (U/L) >=3 x ULN	Aspartate Aminotransferase (U/L)
5	0	Bicarbonate		Bicarbonate (mmol/L)
5	1	<=18 mmol/L	Bicarbonate <=18 mmol/L	Bicarbonate (mmol/L)
5	2	>=30 mmol/L	Bicarbonate >=30 mmol/L	Bicarbonate (mmol/L)
6	1	Bilirubin, Total >=2.0 mg/dL	Bilirubin, Total >=2.0 mg/dL	Bilirubin (mg/dL)
7	1	Blood Urea Nitrogen >30 mg/dL	Blood Urea Nitrogen >30 mg/dL	Blood Urea Nitrogen (mg/dL)
8	0	Calcium		Calcium (mg/dL)
8	1	<7 mg/dL	Calcium <7 mg/dL	Calcium (mg/dL)
8	2	>12 mg/dL	Calcium >12 mg/dL	Calcium (mg/dL)
9	1	Cholesterol, Total >300 mg/dL	Cholesterol, Total >300 mg/dL	Cholesterol (mg/dL)
10	1	Creatine Kinase (U/L) >3 x ULN	Creatine Kinase (U/L) >3 x ULN	Creatine Kinase (U/L)
11	0	Chloride		Chloride (mmol/L)
11	1	<=90 mmol/L	Chloride <=90 mmol/L	Chloride (mmol/L)
11	2	>=118 mmol/L	Chloride >=118 mmol/L	Chloride (mmol/L)
12	1	Creatinine >=2.0 mg/dL	Creatinine >=2.0 mg/dL	Creatinine (mg/dL)
13	1	Gamma Glutamyl Transferase (U/L) >=3 x ULN	Gamma Glutamyl Transferase (U/L) >=3 x ULN	Gamma Glutamyl Transferase (U/L)
14	0	Glucose		Glucose (mg/dL)
14	1	<50 mg/dL	Glucose <50 mg/dL	Glucose (mg/dL)
14	2	>200 mg/dL	Glucose >200 mg/dL	Glucose (mg/dL)
15	1	HDL Cholesterol <=30 mg/dL	HDL Cholesterol <=30 mg/dL	HDL Cholesterol (mg/dL)
16	0	Potassium		Potassium (mmol/L)
16	1	<3 mmol/L	Potassium <3 mmol/L	Potassium (mmol/L)
16	2	>5.5 mmol/L	Potassium >5.5 mmol/L	Potassium (mmol/L)
17	1	Lactate Dehydrogenase (U/L) >3 x ULN	Lactate Dehydrogenase (U/L) >3 x ULN	Lactate Dehydrogenase (U/L)
18	1	LDL Cholesterol >=160 mg/dL	LDL Cholesterol >=160 mg/dL	LDL Cholesterol (mg/dL)
19	0	Phosphate		Phosphate (mg/dL)
19	1	<2 mg/dL	Phosphate <2 mg/dL	Phosphate (mg/dL)
19	2	>5 mg/dL	Phosphate >5 mg/dL	Phosphate (mg/dL)
20	1	Prolactin (ng/mL) >1 x ULN	Prolactin (ng/mL) >1 x ULN	Prolactin (ng/mL)
21	0	Sodium		Sodium (mmol/L)
21	1	<130 mmol/L	Sodium <130 mmol/L	Sodium (mmol/L)
21	2	>150 mmol/L	Sodium >150 mmol/L	Sodium (mmol/L)
22	0	Triglycerides		Triglycerides (mg/dL)
22	1	>=120 mg/dL (Female)	Triglycerides >=120 mg/dL (Female)	Triglycerides (mg/dL)
22	2	>=160 mg/dL (Male)	Triglycerides >=160 mg/dL (Male)	Triglycerides (mg/dL)
23	1	Thyrotropin >5.5 uIU/mL	Thyrotropin >5.5 uIU/mL	Thyrotropin (uIU/mL)
24	0	Urate		Urate (mg/dL)
24	1	Urate >9 mg/dL	Urate >9 mg/dL	Urate (mg/dL)
25	0	Urate		Urate (mg/dL)
25	1	Urate >8 mg/dL (Female)	Urate >8 mg/dL (Female)	Urate (mg/dL)
25	2	Urate >10 mg/dL (Male)	Urate >10 mg/dL (Male)	Urate (mg/dL)

Display 4. PCS Criteria Template

_ORD1	_ORD2	_ROWTEXT	_CRIT	PARAM	SOURCE	_npct1	_npct2	_npct3
1	1	Albumin <2.5 g/dL	Albumin <2.5 g/dL	Albumin (g/dL)		0/97	0/18	0/20
2	1	Alkaline Phosphatase (U/L) >=3 x ULN	Alkaline Phosphatase (U/L) >=3 x ULN	Alkaline Phosphatase (U/L)		0/97	0/18	0/20
3	1	Alanine Aminotransferase (U/L) >=3 x ULN	Alanine Aminotransferase (U/L) >=3 x ULN	Alanine Aminotransferase (U/L)		0/97	0/18	0/19
4	1	Aspartate Aminotransferase (U/L) >=3 x ULN	Aspartate Aminotransferase (U/L) >=3 x ULN	Aspartate Aminotransferase (U/L)		0/97	0/18	0/20
5	0	Bicarbonate		Bicarbonate (mmol/L)				
5	1	@R/RTF'\fi-200\li200'<=18 mmol/L	Bicarbonate <=18 mmol/L	Bicarbonate (mmol/L)		0/97	0/18	0/20
5	2	@R/RTF'\fi-200\li200'>=30 mmol/L	Bicarbonate >=30 mmol/L	Bicarbonate (mmol/L)		0/96	0/18	0/20

A Methodology of Laboratory Data Reporting of Potentially Clinical Significant Abnormality (PCSA) for Clinical Study Report, continued

6	1	Bilirubin, Total >=2.0 mg/dL	Bilirubin, Total >=2.0 mg/dL	Bilirubin (mg/dL)		0/97	0/18	0/20
7	1	Blood Urea Nitrogen >30 mg/dL	Blood Urea Nitrogen >30 mg/dL	Blood Urea Nitrogen (mg/dL)		0/97	0/18	0/20
8	0	Calcium		Calcium (mg/dL)				
8	1	@R/RTF'\fi-200\li200'<7 mg/dL	Calcium <7 mg/dL	Calcium (mg/dL)		0/97	0/18	0/20
8	2	@R/RTF'\fi-200\li200'>12 mg/dL	Calcium >12 mg/dL	Calcium (mg/dL)		0/97	0/18	0/20
9	1	Cholesterol, Total >300 mg/dL	Cholesterol, Total >300 mg/dL	Cholesterol (mg/dL)	**CRIT2**	2/96 (2.1)	0/18	1/20 (5.0)
10	1	Creatine Kinase (U/L) >3 x ULN	Creatine Kinase (U/L) >3 x ULN	Creatine Kinase (U/L)	CRIT2	1/95 (1.1)	1/18 (5.6)	1/20 (5.0)
11	0	Chloride		Chloride (mmol/L)				
11	1	@R/RTF'\fi-200\li200'<=90 mmol/L	Chloride <=90 mmol/L	Chloride (mmol/L)		0/97	0/18	0/20
11	2	@R/RTF'\fi-200\li200'>=118 mmol/L	Chloride >=118 mmol/L	Chloride (mmol/L)		0/97	0/18	0/20
12	1	Creatinine >=2.0 mg/dL	Creatinine >=2.0 mg/dL	Creatinine (mg/dL)		0/97	0/18	0/20
13	1	Gamma Glutamyl Transferase (U/L) >=3 x ULN	Gamma Glutamyl Transferase (U/L) >=3 x ULN	Gamma Glutamyl Transferase (U/L)		0/93	0/18	0/19
14	0	Glucose		Glucose (mg/dL)				
14	1	@R/RTF'\fi-200\li200'<50 mg/dL	Glucose <50 mg/dL	Glucose (mg/dL)		0/97	0/18	0/20
14	2	@R/RTF'\fi-200\li200'>200 mg/dL	Glucose >200 mg/dL	Glucose (mg/dL)	CRIT2	1/96 (1.0)	0/18	0/20
15	1	HDL Cholesterol <=30 mg/dL	HDL Cholesterol <=30 mg/dL	HDL Cholesterol (mg/dL)	CRIT1	1/96 (1.0)	0/16	0/19
16	0	Potassium		Potassium (mmol/L)				
16	1	@R/RTF'\fi-200\li200'<3 mmol/L	Potassium <3 mmol/L	Potassium (mmol/L)		0/97	0/18	0/20
16	2	@R/RTF'\fi-200\li200'>5.5 mmol/L	Potassium >5.5 mmol/L	Potassium (mmol/L)	CRIT2	3/97 (3.1)	0/18	0/20
17	1	Lactate Dehydrogenase (U/L) >3 x ULN	Lactate Dehydrogenase (U/L) >3 x ULN	Lactate Dehydrogenase (U/L)		0/97	0/18	0/20
18	1	LDL Cholesterol >=160 mg/dL	LDL Cholesterol >=160 mg/dL	LDL Cholesterol (mg/dL)	CRIT2	6/80 (7.5)	1/17 (5.9)	1/16 (6.3)
19	0	Phosphate		Phosphate (mg/dL)				
19	1	@R/RTF'\fi-200\li200'<2 mg/dL	Phosphate <2 mg/dL	Phosphate (mg/dL)		0/97	0/18	0/20
19	2	@R/RTF'\fi-200\li200'>5 mg/dL	Phosphate >5 mg/dL	Phosphate (mg/dL)	CRIT2	0/96	1/18 (5.6)	0/20
20	1	Prolactin (ng/mL) >1 x ULN	Prolactin (ng/mL) >1 x ULN	Prolactin (ng/mL)	CRIT2	1/92 (1.1)	0/16	0/19
21	0	Sodium		Sodium (mmol/L)				
21	1	@R/RTF'\fi-200\li200'<130 mmol/L	Sodium <130 mmol/L	Sodium (mmol/L)		0/97	0/18	0/20
21	2	@R/RTF'\fi-200\li200'>150 mmol/L	Sodium >150 mmol/L	Sodium (mmol/L)		0/97	0/18	0/20
22	0	Triglycerides		Triglycerides (mg/dL)				
22	1	@R/RTF'\fi-200\li200'>=120 mg/dL (Female)	Triglycerides >=120 mg/dL (Female)	Triglycerides (mg/dL)	CRIT2	14/54 (25.9)	2/12 (16.7)	1/12 (8.3)
22	2	@R/RTF'\fi-200\li200'>=160 mg/dL (Male)	Triglycerides >=160 mg/dL (Male)	Triglycerides (mg/dL)	CRIT2	3/54 (5.6)	2/12 (16.7)	1/12 (8.3)
23	1	Thyrotropin >5.5 uIU/mL	Thyrotropin >5.5 uIU/mL	Thyrotropin (uIU/mL)		0/ 0	0/ 0	0/ 0
24	0	Urate		Urate (mg/dL)				
24	1	@R/RTF'\fi-200\li200'Urate >9	Urate >9 mg/dL	Urate (mg/dL)	CRIT2	0/96	0/18	0/20

		mg/dL						
25	0	Urate		Urate (mg/dL)				
25	1	@R/RTF'\fi-200\li200'Urate >8 mg/dL (Female)	Urate >8 mg/dL (Female)	Urate (mg/dL)		0/97	0/18	0/20
25	2	@R/RTF'\fi-200\li200'Urate >10 mg/dL (Male)	Urate >10 mg/dL (Male)	Urate (mg/dL)	CRIT3	1/97 (1.0)	0/18	0/20

Display 5. An Example of Dataset (final) before PCSA Table Outputting with Template

The final PCSA table with a template can be shown in Display 6. All PCSA categories are listed in this table.

Company Name Page 1 of 3
Study No. XXX-yyy

Table 14.3.4.3.1
Number (Percentage) of Subjects with Potentially Clinically Significant (PCS) Values in Chemistry at Any Post-Baseline Visit during Stage 1 Safety Period
- Entire Safety Population

	Stage 1 Treatment Group		
Parameter / PCS Criteria	Treatment A (N=97) n/m (%)	Treatment B (N=21) n/m (%)	Treatment C (N=21) n/m (%)
Albumin <2.5 g/dL	0/97	0/18	0/20
Alkaline Phosphatase (U/L) >=3 x ULN	0/97	0/18	0/20
Alanine Aminotransferase (U/L) >=3 x ULN	0/97	0/18	0/19
Aspartate Aminotransferase (U/L) >=3 x ULN	0/97	0/18	0/20
Bicarbonate			
<=18 mmol/L	0/97	0/18	0/20
>=30 mmol/L	0/96	0/18	0/20
Bilirubin, Total >=2.0 mg/dL	0/97	0/18	0/20
Blood Urea Nitrogen >30 mg/dL	0/97	0/18	0/20
Calcium			
<7 mg/dL	0/97	0/18	0/20
>12 mg/dL	0/97	0/18	0/20
Cholesterol, Total >300 mg/dL	2/96 (2.1)	0/18	1/20 (5.0)

n is the number of subjects who met the PCS criteria. m is the number of subjects with non-PCS baseline and at least one post-baseline assessment
Source Data: Listing 16.2.8.1.2

Display 6. An Example of PCSA Table with Template

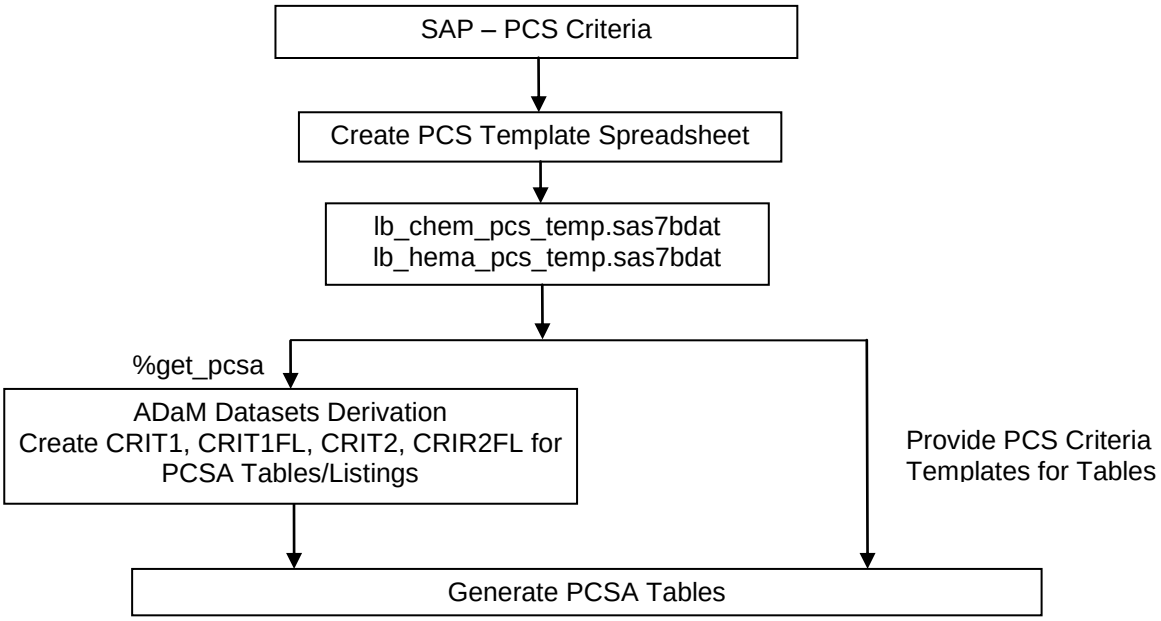
The sample code to create PCS criteria Template for Serum Chemistry Lab Tests is as below.

```
proc sort data = adlb out = shell(keep=paramcd param) nodupkey;
      by paramcd param;
      where paramcd in ('ALB','ALT','ALP','AST','BICARB','BUN','CA','CK','CL','CREAT','GLUC','GGT','HDL','LDH','LDL','PHOS',
                        'K','PROLCTN','SODIUM','BILI','CHOL','TRIG','TSH','URATE','HCT','HGB','NEUT','PLAT','WBC','EOS');
run;
data shell1;
      set shell;
      length _rowtext _crit $200;
      if paramcd='ALB' then do;              *** PCS Categories for ALB ***;
         _ord1 = 1; _crit = 'Albumin <2.5 g/dL';  _rowtext = strip(_crit);  _ord2 = 1; output;
      end;
      if paramcd='ALP' then do;              *** PCS Categories for ALP ***;
         _ord1 = 2; _crit = 'Alkaline Phosphatase (U/L) >=3 x ULN';  _rowtext = strip(_crit);  _ord2 = 1; output;
      end;
```

```
      if paramcd='ALT' then do;                *** PCS Categories for ALT ***;
         _ord1 = 3; _crit = 'Alanine Aminotransferase (U/L) >=3 x ULN';  _rowtext = strip(_crit);  _ord2 = 1; output;
      end;
      if paramcd='AST' then do;                *** PCS Categories for AST ***;
        _ord1 = 4; _crit = 'Aspartate Aminotransferase (U/L) >=3 x ULN';  _rowtext = strip(_crit);  _ord2 = 1; output;
      end;
     if paramcd='BICARB' then do;              *** PCS Categories for BICARB ***;
        _ord1 = 5;
        _crit = '';  _rowtext = 'Bicarbonate';  _ord2 = 0; output;
        _crit = 'Bicarbonate <=18 mmol/L'; _rowtext = "<=18 mmol/L";  _ord2 = 1; output;
        _crit = 'Bicarbonate >=30 mmol/L'; _rowtext = ">=30 mmol/L";  _ord2 = 2; output;
     end;
     if paramcd='BILI' then do;               *** PCS Categories for BILI ***;
       _ord1 = 6; _crit = 'Bilirubin, Total >=2.0 mg/dL';  _rowtext = strip(_crit);  _ord2 = 1; output;
     end;
     if paramcd= 'BUN' then do;               *** PCS Categories for BUN ***;
        _ord1 = 7; _crit = 'Blood Urea Nitrogen >30 mg/dL';  _rowtext = strip(_crit);  _ord2 = 1; output;
     end;
      if paramcd= 'CA' then do;               *** PCS Categories for CA ***;
        _ord1 = 8;
        _crit = '';  _rowtext = 'Calcium';  _ord2 = 0; output;
        _crit = 'Calcium <7 mg/dL'; _rowtext = "<7 mg/dL";  _ord2 = 1; output;
        _crit = 'Calcium >12 mg/dL'; _rowtext = ">12 mg/dL";  _ord2 = 2; output;
      end;
      if paramcd= 'CHOL' then do;             *** PCS Categories for CHOL ***;
        _ord1 = 9; _crit = 'Cholesterol, Total >300 mg/dL';  _rowtext = strip(_crit);  _ord2 = 1; output;
      end;
…
    if paramcd= 'URATE' then do;              *** PCS Categories for URATE ***;
      _ord1 = 24;
     _crit = '';  _rowtext = 'Urate';  _ord2 = 0; output;
     _crit = 'Urate >9 mg/dL';  _rowtext = '>9 mg/dL';  _ord2 = 1; output;
      _ord1 = 25; fromcrit3 = 1;
     _crit = '';  _rowtext = 'Urate';  _ord2 = 0; output;
     _crit = 'Urate >8 mg/dL (Female)';  _rowtext = '>8 mg/dL (Female)';  _ord2 = 1; output;
     _crit = 'Urate >10 mg/dL (Mmale)';  _rowtext = '>10 mg/dL (Male)';  _ord2 = 2; output;
   end;
run;
proc sort data=shell1; by paramcd param _crit; run;
data pcs;
      merge shell1(in=a) allpcs2(in=b));
      by paramcd param _crit;
      if a;
run;
data final1;  *** Generate Final Dataset for PCSA Table Output ***;
      merge pcs(in=a) total1 toal2 total3; by paramcd param;
      if a;
      length _npct1-_npct3 $40;
      array col[3] _npct1-_npct3;   array count[3] trt1-trt3;  array tot[3] tot1-tot3;
      array tot1_[3] tot1_1-tot1_3; array tot2_[3] tot2_1-tot2_3; array tot3_[3] tot3_1-tot3_3;
      if _ord2 > 0 then do;
         do i = 1 to 3;
            if not missing(crit1_org_unit) then tot[i]=tot1_[i];
            if not missing(crit2_org_unit) and missing(fromcrit3) then tot[i]=tot2_[i];
            if not missing(crit2_org_unit) and fromcrit3 then tot[i]=tot3_[i];              if count[i] in (., 0) then count[i] = 0;  if tot[i] in (., 0)
then tot[i] = 0;
            if count[i] = 0 then col[i] = '  0/' || put(tot[i], 2.);
           else then col[i] = put(count[i], 2.0) || '/' || put(tot[i], 2.) || ' (' || put(100*count[i]/tot[i], 5.1) || ')';
         end;
      end;
      keep  _ord1 _ord2 _rowtext _crit _npct1-_npct3 paramcd;
run;
proc sort data=final1; by _ord1 _ord2; run;
data final; *** Adjust the format ***;
      set final1;
      by _ord1 _ord2;
      if not first._ord1 then _rowtext = "  @R/RTF'\fi-200\li200' " || strip(_rowtext);
run;
```

NEW METHODOLOGY FOR GENERATING PCSA TABLES

Usually there are a lot of PCS criteria defined in SAP shown above. For example, one of our studies has totally 44 PCS criteria defined for 30 Lab Parameters of CHEMISTRY and HEMATOLOGY. The general method to create PCSA tables contains a lot of manual work, including ADaM Programming for PCS criteria variables, and Table Programming for PCS Criteria Templates, which have been shown above. As PCS criteria are study specific and may be different in a new study, it is very labor-intensive and error-prone to manually create PCS criteria variables in ADLB programming or generate PCS Criteria Templates in PCS table programming. Frequent changes in lab tests collected in different studies add more complexity into the general method. We developed a new methodology to automate the process to generate PCS variables in ADaM programming and PCS Criteria Template in Table Programming. Display 7 shows the process flow for new methodology of PCS Programming.



Display 7. Overview of Process Flow for New Methodology of PCS Programming

PCS CRITERIA TEMPLATE

Based on our new methodology, a spreadsheet will be created to incorporate PCS criteria in SAP for selected parameters of Serum Chemistry and Hematology with ADaM PCS variable generation rules and PCS Criteria Templates.

The PCS Criteria Template spreadsheet is designed, and shown in Display 8.

Selected	Parameter Category 1	Parameter Code	Parameter	Original Units	Analysis Criteria (CRIT1 or CRIT2)	Criterion 1 in Conventional Unit (CRIT1)	Criterion 2 in Conventional Unit (CRIT2)	Row Label for Table
Y	CHEMISTRY	ALB	Albumin (g/dL)	g/dL	Albumin <2.5 g/dL	PARAMCD = 'ALB' and LBORRESU = 'g/dL' and .<AVAL<2.5		Albumin <2.5 g/dL
Y	CHEMISTRY	ALP	Alkaline Phosphatase (U/L)	U/L	Alkaline Phosphatase (U/L) >=3 x ULN		PARAMCD = 'ALP' and LBORRESU = 'U/L' and AVAL>=3*ANRHI	Alkaline Phosphatase (U/L) >=3 x ULN
	CHEMISTRY	ALP	Alkaline Phosphatase (U/L)	U/L	Alkaline Phosphatase (U/L) >=5 x ULN		PARAMCD = 'ALP' and l LBORRESU = 'U/L' and AVAL>=5*ANRHI	Alkaline Phosphatase (U/L) >=5 x ULN
Y	CHEMISTRY	ALT	Alanine Aminotransferase (U/L)	U/L	Alanine Aminotransferase (U/L) >=3 x ULN		PARAMCD = 'ALT' and LBORRESU = 'U/L' and AVAL>=3*ANRHI	Alanine Aminotransferase (U/L) >=3 x ULN
	CHEMISTRY	ALT	Alanine Aminotransferase (U/L)	U/L	Alanine Aminotransferase (U/L) >=5 x ULN		PARAMCD = 'ALT' and LBORRESU = 'U/L' and AVAL>=5*ANRHI	Alanine Aminotransferase (U/L) >=5 x ULN
Y	CHEMISTRY	AST	Aspartate Aminotransferase (U/L)	U/L	Aspartate Aminotransferase (U/L) >=3 x ULN		PARAMCD = 'AST' and LBORRESU = 'U/L' and AVAL>=3*ANRHI	Aspartate Aminotransferase (U/L) >=3 x ULN
	CHEMISTRY	AST	Aspartate Aminotransferase (U/L)	U/L	Aspartate Aminotransferase (U/L) >=5 x ULN		PARAMCD = 'AST' and LBORRESU = 'U/L' and AVAL>=5*ANRHI	Aspartate Aminotransferase (U/L) >=5 x ULN

Y	CHEMISTRY	BICARB	Bicarbonate (mmol/L)	mmol/L				Bicarbonate
Y	CHEMISTRY	BICARB	Bicarbonate (mmol/L)	mmol/L	Bicarbonate <=18 mmol/L	PARAMCD='BICARB' and LBORRESU='mmol/L' and .Z<AVAL<=18		<=18 mmol/L
Y	CHEMISTRY	BICARB	Bicarbonate (mmol/L)	mmol/L	Bicarbonate >=30 mmol/L		PARAMCD='BICARB' and LBORRESU='mmol/L' and AVAL>=30	>=30 mmol/L
Y	CHEMISTRY	BILI	Bilirubin (mg/dL)	mg/dL	Bilirubin, Total >=2.0 mg/dL		PARAMCD = 'BILI' and LBORRESU = 'mg/dL' and AVAL>=2.0	Bilirubin, Total >=2.0 mg/dL
Y	CHEMISTRY	BUN	Blood Urea Nitrogen (mg/dL)	mg/dL	Blood Urea Nitrogen >30 mg/dL		PARAMCD = 'BUN' and LBORRESU = 'mg/dL' and AVAL>30	Blood Urea Nitrogen >30 mg/dL
Y	CHEMISTRY	CA	Calcium (mg/dL)	mg/dL				Calcium
Y	CHEMISTRY	CA	Calcium (mg/dL)	mg/dL	Calcium <7 mg/dL	PARAMCD = 'CA' and LBORRESU = 'mg/dL' and .<AVAL<7		<7 mg/dL
Y	CHEMISTRY	CA	Calcium (mg/dL)	mg/dL	Calcium >12 mg/dL		PARAMCD = 'CA' and LBORRESU = 'mg/dL' and AVAL>12	>12 mg/dL

Display 8. PCS Criteria Template Spreadsheet (Chemistry)

A separate worksheet is created for each Parameter Category such as Chemistry and Hematology. PCS criteria from all existing studies will be populated into each worksheet.

The first column, **Selected**, will be used to select criteria for a certain parameter in a specific study. Only selected one will be shown in the PCSA tables. The columns **Parameter Category1**, **Parameter**, and **Original Units**, together identify the selected parameters for which PCS criteria apply. The column **Analysis Criteria (CRIT1 or CRIT2)** contains PCS criteria for variables CRIT1 or CRIT2. Column **Criterion 1 in Conventional Unit (CRIT1)** defines the complete programming rule for PCS criteria variable CRIT1, and **Criterion 2 in Conventional Unit (CRIT2)** for PCS criteria variable CRIT2. Column **Row Label for Table** presents the text for each PCS category in a final PCSA table.

The contents of PCS Criteria Template spreadsheet will be imported to SAS datasets for ADaM programming and Table programming use as shown in Display 9.

SELECTED	_ORD1	_ORD2	_ROWTEXT	_CRIT	PARCAT1	PARAMCD	PARAM	LBORRESU	CRIT1_ORG_UNIT	CRIT2_ORG_UNIT
Y	1	1	Albumin <2.5 g/dL	Albumin <2.5 g/dL	CHEMISTRY	ALB	Albumin (g/dL)	g/dL	PARAMCD = 'ALB' and LBORRESU = 'g/dL' and .<AVAL<2.5	
Y	2	1	Alkaline Phosphatase (U/L) >=3 x ULN	Alkaline Phosphatase (U/L) >=3 x ULN	CHEMISTRY	ALP	Alkaline Phosphatase (U/L)	U/L		PARAMCD = 'ALP' and LBORRESU = 'U/L' and AVAL>=3*ANRHI
	.	.	Alkaline Phosphatase (U/L) >=5 x ULN	Alkaline Phosphatase (U/L) >=5 x ULN	CHEMISTRY	ALP	Alkaline Phosphatase (U/L)	U/L		PARAMCD = 'ALP' and l LBORRESU = 'U/L' and AVAL>=5*ANRHI
Y	3	1	Alanine Aminotransferase (U/L) >=3 x ULN	Alanine Aminotransferase (U/L) >=3 x ULN	CHEMISTRY	ALT	Alanine Aminotransferase (U/L)	U/L		PARAMCD = 'ALT' and LBORRESU = 'U/L' and AVAL>=3*ANRHI
	.	.	Alanine Aminotransferase (U/L) >=5 x ULN	Alanine Aminotransferase (U/L) >=5 x ULN	CHEMISTRY	ALT	Alanine Aminotransferase (U/L)	U/L		PARAMCD = 'ALT' and LBORRESU = 'U/L' and AVAL>=5*ANRHI
Y	4	1	Aspartate Aminotransferase (U/L) >=3 x ULN	Aspartate Aminotransferase (U/L) >=3 x ULN	CHEMISTRY	AST	Aspartate Aminotransferase (U/L)	U/L		PARAMCD = 'AST' and LBORRESU = 'U/L' and AVAL>=3*ANRHI
	.	.	Aspartate Aminotransferase (U/L) >=5 x ULN	Aspartate Aminotransferase (U/L) >=5 x ULN	CHEMISTRY	AST	Aspartate Aminotransferase (U/L)	U/L		PARAMCD = 'AST' and LBORRESU = 'U/L' and AVAL>=5*ANRHI
Y	5	1	Bilirubin, Total >=2.0 mg/dL	Bilirubin, Total >=2.0 mg/dL	CHEMISTRY	BILI	Bilirubin (mg/dL)	mg/dL		PARAMCD = 'BILI' and LBORRESU = 'mg/dL' and AVAL>=2.0
Y	6	1	Blood Urea Nitrogen >30 mg/dL	Blood Urea Nitrogen >30 mg/dL	CHEMISTRY	BUN	Blood Urea Nitrogen (mg/dL)	mg/dL		PARAMCD = 'BUN' and LBORRESU = 'mg/dL' and AVAL>30
Y	7	0	Calcium		CHEMISTRY	CA	Calcium (mg/dL)	mg/dL		
Y	7	1	<7 mg/dL	Calcium <7 mg/dL	CHEMISTRY	CA	Calcium (mg/dL)	mg/dL	PARAMCD = 'CA' and LBORRESU = 'mg/dL' and .<AVAL<7	
Y	7	2	>12 mg/dL	Calcium >12 mg/dL	CHEMISTRY	CA	Calcium (mg/dL)	mg/dL		PARAMCD = 'CA' and LBORRESU = 'mg/dL' and AVAL>12

Display 9. An Example of PCS Criteria Template Dataset (LB_CHEM_PCS_TEMP)

PCS Criteria Template datasets contain all the information in PCS Criteria Template spreadsheet. Each column in the spreadsheet will be transferred to a SAS data variable. The one to one mapping can be seen in table 3. Additionally,

two more variables _ORD1 and _ORD2 are generated automatically by the importing program for the sorting order of the PCS categories in PCSA tables, in which _ORD1 provides the order of each parameter, and _ORD2 provides the order of subcategories within each parameter.

SAS Variables	Column Header in Spreadsheet	Comment
SELECTED	Selected	Select/Unselect PCS criterion
_ORD1		Sort PCS criteria data by SELECTED and PARAMCD, _ORD1 is the order of each parameter
_ORD2		Sort PCS criteria data by SELECTED and PARAMCD, _ORD2 is the order within each parameter
_ROWTEXT	Row Label for Table	Row text for Each PCS category in PCSA table
_CRIT	Analysis Criteria (CRIT1 or CRIT2)	PCS criterion for ADaM variables CRIT1, CRIT2/CRIT3
PARCAT1	Parameter Category 1	Identify selected parameter category
PARAMCD	Parameter Code	Identify selected parameter code
PARAM	Parameter	Identify selected parameter
LBORRESU	Original Units	Identify original unit of the selected parameter
CRIT1_ORG_UNIT	Criterion 1 in Conventional Unit (CRIT1)	Programming rule for PCS variable CRIT1
CRIT2_ORG_UNIT	Criterion 2 in Conventional Unit (CRIT2)	Programming rule for PCS variable CRIT2/CRIT3

Table 3. One to One Mapping from Spreadsheet Columns to SAS Variables

AUTOMATIC CREATION OF PCS VARIABLES IN ADAM DATASETS

In ADLB, criteria variables CRIT1 and CRIT2/CRIT3 are designed to for PCS criteria related to abnormal low values and the abnormal high values. As there are a large number of laboratory parameters with PCS criteria, which may vary in each individual study, it is desirable to automatically populate those PCS criteria variables in ADLB dataset. A macro **%pcsa was developed to** automatically read the PCS Criteria Template datasets, generate macro variables for PCS criteria and action taken when the criteria are satisfied, and insert code into DATA step for deriving PCS criteria variables CRIT1 and CRIT2/CRIT3. The code can be shown as below:

```
%macro pcsa(datain=,dataout=);
data pcsa_mvar;   *** PCS criteria ***;
      set external.lb_chem_pcs_temp(where=(selected='Y'))
          external.lb_hema_pcs_temp(where=(selected='Y')) end=eof;
      by parcat1 paramcd _ord1 _ord2;
      length _rowtext1 $200;
      retain numcrit flg 0 _rowtext1;
      if first.paramcd then do; _rowtext1 = strip(_rowtext); flg = 0; end;
      else if (_rowtext1 = _rowtext) or (index(_rowtext1,'>') and index(_rowtext,'>') and
      index(_rowtext, 'Female')=0 and index(_rowtext, 'Male'=0)) then flg = 1; ** flg = 1 if multiple criteria for PCS-High **;
      if not missing(crit1_org_unit) then do; numcrit + 1;
        call symput('crit'||strip(put(numcrit,best.)),strip(crit1_org_unit));
        call symput('act'||strip(put(numcrit,best.)),"crit1fl='Y'; crit1='" || strip(_sublabel) || "'");
      end;
      else if not missing(crit2_org_unit) then do;
              numcrit + 1;
              call symput('crit'||strip(put(numcrit,best.)),strip(crit2_org_unit));
              if flg=0 then call symput('act'||strip(put(numcrit,best.)),"crit2fl='Y'; crit2='" || strip(_sublabel) || "'");
              if flg=1 then call symput('act'||strip(put(numcrit,best.)),"crit3fl='Y'; crit3='" || strip(_sublabel) || "'");
      end;
      if eof then call symput('numcrit',strip(put(numcrit,best.)));
run;
proc sort data = pcsa_mvar;by parcat1 paramcd param lborresu;run;
data &dataout.;
      length crit1fl crit2fl crit3fl $1. crit1 crit2 crit3 $100;
      set &datain.;
      %do i = 1 %to &numcrit.;
              if &&crit&i. then do; &&act&i.;end;
      %end;
run;
%mend;
```

Three sets of Global Macro Variables are generated from PCS Criteria Template Data:

1. &numcrit: Store the number of PCS criteria defined in SAP
2. &&crit&i: Store the SAS code to Identify whether PCS criteria are Satisfied from CRIT1_ORG_UNIT and CRIT2_ORG_UNIT

3. &&act&i: Store the SAS code to define CRIT1, CRIT1FL, or CRIT2, CRIT2FL (or CRIT3, CRIT3FL) from _CRIT for CRIT1 or CRIT2 (or CRIT3) and set CRIT1FL or CRIT2FL (or CRIT3FL) to 'Y'

They are used for automatically create PCS variables in ADaM. The ADaM Dataset with PCS variables can be shown in Display 1.

In order to avoid human errors from creation of PCS Criteria Template spreadsheet, the above macro **%pcsa** has been developed to automatically check whether laboratory parameters defined in PCS Criteria Template spreadsheet exist in laboratory analysis datasets.

```
proc freq data=&datain. noprint;
      tables parcat1*paramcd*param*lborresu/out=param_data(drop=percent);
      where lbstat^='NOT DONE';
run;

data in_pcsa_only in_data_only;
      merge pcsa_mvar(in=a) param_data(in=b where=(parcat1 in ('HEMATOLOGY','CHEMISTRY')));
      by parcat1 paramcd param lborresu;
      if a and not b and first.param then do;
         put 'WARN' 'ING: PARAMCD = 'paramcd' , PARAM = 'param' is not in the dataset, please double check your PCS template!';
         output in_pcsa_only;
      end;
      if b and not a then output in_data_only;
run;
```

The erroneous laboratory parameters will be picked up in SAS data in_pcsa_only as shown in Display 10. And Display 11 is an example log file when a laboratory parameter was accidentally selected in PCS template dataset while it was not in ADLB. Actions are needed to double check the laboratory parameters in PCS template spreadsheet when we found the warnings in the log file and data in_pcsa_only is not empty.

SELECTED	_ORD1	_ORD2	_ROWTEXT	_CRIT	PARCAT1	PARAMCD	PARAM	LBORRESU	CRIT1_ORG_UNIT	CRIT2_ORG_UNIT
Y	19	0	Phosphate		CHEMISTRY	PHOS	Phosphorus (mg/dL)	mg/dL		
Y	19	1	<2 mg/dL	Phosphate <2 mg/dL	CHEMISTRY	PHOS	Phosphorus (mg/dL)	mg/dL	PARAMCD = 'PHOS' and LBORRESU = 'mg/dL' and .<AVAL<2	
Y	19	2	>5 mg/dL	Phosphate >5 mg/dL	CHEMISTRY	PHOS	Phosphorus (mg/dL)	mg/dL		PARAMCD = 'PHOS' and LBORRESU = 'mg/dL' and AVAL>5

Display 10. Example SAS data in_pcsa_only when a laboratory parameter is in PCS Template Datasets, but not in ADLB

```
MPRINT(PCSA):   data in_pcsa_only in_data_only;
MPRINT(PCSA):   merge pcsa_mvar(in=a) param_data(in=b where=(parcat1 in
('HEMATOLOGY','CHEMISTRY')));
MPRINT(PCSA):   by parcat1 paramcd param lborresu;
MPRINT(PCSA):   if a and not b and first.param then do;
MPRINT(PCSA):   put 'WARN' 'ING: PARAMCD = ' paramcd ' , PARAM = ' param ' is not in the dataset,
please double check your PCSA template!';
MPRINT(PCSA):   output in_pcsa_only;
MPRINT(PCSA):   end;
MPRINT(PCSA):   if b and not a then output in_data_only;
MPRINT(PCSA):   run;

WARNING: PARAMCD = PHOS   , PARAM = Phosphorus (mg/dL)  is not in the dataset, please double check
your PCSA template!
NOTE: There were 43 observations read from the data set WORK.PCSA_MVAR.
NOTE: There were 43 observations read from the data set WORK.PARAM_DATA.
      WHERE parcat1 in ('CHEMISTRY', 'HEMATOLOGY');
NOTE: The data set WORK.IN_PCSA_ONLY has 3 observations and 14 variables.
NOTE: The data set WORK.IN_DATA_ONLY has 19 observations and 14 variables.
NOTE: DATA statement used (Total process time):
      real time           0.00 seconds
      cpu time            0.00 seconds
```

Display 11. Example log file when a laboratory parameter is in PCS Template Dataset, but not in ADLB

After reviewing PCS template spreadsheet, we found the reason for the error, which is that the lab tests were updated to standard CDISC/NCI controlled terminology (LBTEST changed from 'Phosphorus' to 'Phosphate') during the study, while PCS template spreadsheet was not updated in time to reflect the change. Action will be taken to change PARAM from Phosphorus (mg/dL) to Phosphate (mg/dL) in PCS Criteria Template Spreadsheet.

Another SAS dataset **in_data_only** will also be generated and shown in Display 12, which contains all CHEMISTRY and HEMATOLOGY laboratory parameters in ADLB while not in PCS template datasets. Programmers should check

against SAP whether these parameters have PCS criteria defined or not, in order to avoid the missing parameters in PCSA tables. This procedure greatly reduces the human errors made in generating PCS template spreadsheet and dramatically improves the quality of the deliverables.

PARCAT1	PARAMCD	PARAM	LBORRESU
CHEMISTRY	HBA1C	Hemoglobin A1C (%)	%
CHEMISTRY	HCG	Choriogonadotropin Beta	
CHEMISTRY	MG	Magnesium (mg/dL)	mg/dL
CHEMISTRY	PHOS	Phosphate (mg/dL)	mg/dL
CHEMISTRY	PROT	Protein (g/dL)	g/dL
HEMATOLOGY	BASO	Basophils (10^3/uL)	10^3/uL
HEMATOLOGY	BASOLE	Basophils/Leukocytes (%)	%
HEMATOLOGY	EOSLE	Eosinophils/Leukocytes (%)	%
HEMATOLOGY	LYM	Lymphocytes (10^3/uL)	10^3/uL
HEMATOLOGY	LYMLE	Lymphocytes/Leukocytes (%)	%
HEMATOLOGY	MONO	Monocytes (10^3/uL)	10^3/uL
HEMATOLOGY	MONOLE	Monocytes/Leukocytes (%)	%
HEMATOLOGY	NEUTLE	Neutrophils/Leukocytes (%)	%
HEMATOLOGY	RBC	Erythrocytes (10^6/uL)	10^6/uL

Display 12. Example SAS data in_data_only when a laboratory parameter is in ADLB, but not in PCS Criteria Template Datasets

PCSA TABLE GENERATION

With PCS Criteria Template, it is possible to automatically create a PCS template when generating PCSA tables as shown in Display 6, which greatly alleviates the burden of manually creating PCS Criteria Template inside PCSA table SAS program. The code can be shown as below:

```
proc sort data = external.lb_chem_pcs_temp(where=(selected='Y')) out=shell1;
      by paramcd param _ord1 _ord2;
run;
data shell1;
      set shell1;
      by paramcd param _ord1 _ord2;
      retain _ord0;
      if first.param then _ord0 = _ord1;
      else if _ord0 ne ord1 then fromcrit3=1;
run;
proc sort data = shell1;by paramcd param _crit;run;
data pcs;
      merge shell1(in=a) allpcs2(in=b);
      by paramcd param _crit;
      if a;
run;
```

With the new methodology, all we need to do for PCSA tables in a new study will be updating study-specific PCS criteria if any changes, and selecting study-specific PCS criteria.

Similarly, we can easily add PCS criteria for ECG and Vital Sign parameters into PCS template spreadsheet, and with the same strategy, generate CDISC-compliant standard variables in ADEG and ADVS for PCS criteria and PCS Criteria Template for PCSA tables.

COMPARISON BETWEEN NEW METHODOLOGY AND GENERAL METHOD

The comparison between new methodology and general method can be summarized in Table 4.

	General Method	**New Method**
First Study with PCS criteria	1. Develop SAS Code for PCS Criteria Variables in ADaM 2. Develop SAS Code to Create a Template for PCS criteria in Table	1. Create a PCS Criteria Template Spreadsheet 2. Build Macro for PCS Criteria Variables in ADaM 3. Apply PCS Criteria Template Data in Table Programming

ADaM Programming	Subject to Frequent Change	No Change
Table Programming	Subject to Frequent Change	No Change
What if PCS Criteria Changed? How to do a New Study with new PCS Criteria?	1. Update SAS Code in ADaM Programming 2. Update SAS Code in Table Programming	1. Select/Unselect PCS Criteria in PCS Criteria Template Spreadsheet 2. No Change for ADaM or Table Programming
Consistency Checking	No	1. Automatically Check Whether Lab Parameters defined in PCS Criteria Template is in ADaM Data 2. Automatically List Lab Parameters in ADaM Data only, and Double Check with SAP PCS Criteria
Manual Work	Labor-Intensive, Error-Prone	Minimal Manual Work with High Quality

Table 4. Comparison between New Methodology and General Method

CONCLUSION

This paper introduces a methodology to develop a standard PCS template spreadsheet library for selected laboratory parameters, and automate the process to generate CDISC-compliant PCS criteria variables in ADLB and PCS Criteria Templates for Lab PCSA tables. With this strategy, while working with other studies, all we need to do is to extend the standard PCS template spreadsheet library and select study-specific PCS criteria. This strategy avoids tedious manual work to create different PCS Criteria Template for PCSA table, minimizes the change of the ADaM and Table programs, and achieves high quality and consistency across the studies.

REFERENCES

1. “Reviewer Guidance -Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review”, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), February 2005

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Appendix 1

An example Criteria of Potentially Clinically Significant (PCS) Abnormality

Category	Parameter	Criteria
Hematology	Hematocrit	≤32% and 3 point decrease from baseline (Female) ≤37% and 3 point decrease from baseline (Male)
	Hemoglobin	≤9.5 g/dL (Female) ≤11.5 g/dL (Male)
	Neutrophils	<1.5 × 10^3/uL
	Platelets	<75.1 × 10^3/uL ≥700 × 10^3/uL
	WBCs	≤2.8 × 10^3/uL ≥16 × 10^3/uL
	Eosinophils	>1.0 × 10^3 cells/uL
Chemistry	Alanine Aminotransferase	≥3 × ULN
	Albumin	<2.5 g/dL
	Alkaline Phosphatase	≥3 × ULN
	Aspartate aminotransferase	≥3 × ULN
	Bicarbonate	≤ 18 mmol/L ≥ 30 mmol/L
	BUN	> 30 mg/dl
	Calcium	<7 mg/dL >12 mg/dL
	Chloride	≤ 90 mmol/L ≥ 118 mmol/L
	Creatine Kinase	>3 × ULN
	Creatinine	≥2 mg/dL
	Gamma Glutamyltransferase	≥3 × ULN
	Glucose	< 50 mg/dL > 200 mg/dL
	HDL Cholesterol	≤ 30 mg/dL
	Lactate Dehydrogenase	>3 × ULN
	LDL Cholesterol	≥160 mg/dL
	Phosphate	<2 mg/dL >5 mg/dL
	Potassium	<3 mmol/L >5.5 mmol/L
	Prolactin	>1 × ULN
	Sodium	<130 mmol/L >150 mmol/L
	Total Bilirubin	≥2 mg/dL
	Total Cholesterol	>300 mg/dL
	Triglycerides	≥120 mg/dL (Female) ≥160 mg/dL (Male)
	TSH	>5.5 uIU/mL
	Uric Acid	> 9 mg/dL > 8 mg/dL (Female) > 10 mg/dL (Male)

LLN = lower limit of normal laboratory reference range; ULN = upper limit of normal laboratory reference range.

Display 13 An Example Criteria of Potentially Clinically Significant (PCS) Abnormality for Selected Analytes

Appendix 2

An Example of PCSA Table Shell

Table 14.3.4.3.1
Number (Percentage) of Subjects with Potentially Clinically Significant (PCS) Values in Chemistry
at Any Post-Baseline Visit during Stage 1 Safety Period
- Entire Safety Population

	Stage 1 Treatment Group		
Parameter / PCS Criteria	Treatment A (N=XX) n/m (%)	Treatment B (N=XX) n/m (%)	Treatment C (N=XX) n/m (%)
Albumin <2.5 g/dL	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Alkaline Phosphatase (U/L) >=3 x ULN	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Alanine Aminotransferase (U/L) >=3 x ULN	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Aspartate Aminotransferase (U/L) >=3 x ULN	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Bicarbonate			
<=18 mmol/L	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
>=30 mmol/L	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Bilirubin, Total >=2.0 mg/dL	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Blood Urea Nitrogen >30 mg/dL	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Calcium			
<7 mg/dL	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
>12 mg/dL	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)
Cholesterol, Total >300 mg/dL	x/xx (xx.x)	x/xx (xx.x)	x/xx (xx.x)

n is the number of subjects who met the PCS criteria. m is the number of subjects with non-PCS baseline and at least one post-baseline assessment
Source Data: Listing 16.2.8.1.2

Appendix 3

An Example of ADLB PCS Variables Design

Variable Name	Variable Label	Type	Length/Display Format	Controlled Terms or Format	Source/Derivation/Comment	Core
CRIT1	Analysis Criterion 1	text	100		Derived: For PARAMCD='ALB' and CRIT1FL='Y', CRIT1='Albumin <2.5 g/dL'; For PARAMCD='BICARB' and CRIT1FL='Y', CRIT1='Bicarbonate <=18 mmol/L'; For PARAMCD='CA' and CRIT1FL='Y', CRIT1='Calcium <7 mg/dL'; For PARAMCD='CL' and CRIT1FL='Y', CRIT1='Chloride <=90 mmol/L'; For PARAMCD='GLUC' and CRIT1FL='Y', CRIT1='Glucose <50 mg/dL'; For PARAMCD='HDL' and CRIT1FL='Y', CRIT1='HDL Cholesterol <=30 mg/dL'; For PARAMCD='PHOS' and CRIT1FL='Y', CRIT1='Phosphate <2 mg/dL'; For PARAMCD='K' and CRIT1FL='Y', CRIT1='Potassium <3 mmol/L'; For PARAMCD='SODIUM' and CRIT1FL='Y', CRIT1='Sodium <130 mmol/L'; For PARAMCD='HCT' and SEX='F' and CRIT1FL='Y', CRIT1='Hematocrit <=32% and 3 point decrease from baseline (Female)'; For PARAMCD='HCT' and SEX='M' and CRIT1FL='Y', CRIT1='Hematocrit <=37% and 3 point decrease from baseline (Male)'; For PARAMCD='HGB' and SEX='F' and CRIT1FL='Y', CRIT1='Hemoglobin <=9.5 g/dL (Female)'; For PARAMCD='HGB' and SEX='M' and CRIT1FL='Y', CRIT1='Hemoglobin <=11.5 g/dL (Male)'; For PARAMCD='NEUT' and CRIT1FL='Y', CRIT1='Neutrophils, Absolute <1.5x10^3/uL'; For PARAMCD='PLAT' and CRIT1FL='Y', CRIT1='Platelets <75.1x10^3/uL'; For PARAMCD='WBC' and CRIT1FL='Y', CRIT1='Leukocytes <=2.8x10^3/uL'	Perm
CRIT1FL	Analysis Criterion 1 Flag	text	1	NYNULL.NY: (1) Y (2) N	Derived: For PARAMCD='ALB' and LBORRESU='g/dL' and .Z<AVAL<2.5, CRIT1FL='Y'; For PARAMCD='BICARB' and LBORRESU='mmol/L' and .Z<AVAL<=18,, CRIT1FL='Y'; For PARAMCD='CA' and LBORRESU='mg/dL' and .Z<AVAL<7, CRIT1FL='Y'; For PARAMCD='CL' and LBORRESU=' mmol/L' and .Z<AVAL<=90, CRIT1='Y'; For PARAMCD='GLUC' and LBORRESU='mg/dL' and .Z<AVAL<50, CRIT1FL='Y'; For PARAMCD='HDL' and LBORRESU='mg/dL' and .Z<AVAL<=30, CRIT1FL='Y' ; For PARAMCD='PHOS' and LBORRESU='mg/dL' and .Z<AVAL<2, CRIT1FL='Y'; For PARAMCD='K' and LBORRESU='mmol/L' and .Z<AVAL<3, CRIT1FL='Y'; For PARAMCD='SODIUM' and LBORRESU='mmol/L' and .Z<AVAL<130, CRIT1FL='Y'; For PARAMCD='HCT' and LBORRESU='%' and SEX='F' and .Z<AVAL<=32 and .Z<CHG<=-3, CRIT1FL='Y'; For PARAMCD='HCT' and LBORRESU='%' and SEX='M' and .Z<AVAL<=37 and .Z<CHG<=-3, CRIT1FL='Y'; For PARAMCD='HGB' and LBORRESU='g/dL' and SEX='F' and .Z<AVAL<=9.5, CRIT1FL='Y'; For PARAMCD='HGB' and LBORRESU='g/dL' and SEX='M' and .Z<AVAL<=11.5, CRIT1FL='Y'; For PARAMCD='NEUT' and LBORRESU='10^3/uL' and .Z<AVAL<1.5, CRIT1FL='Y'; For PARAMCD='PLAT' and LBORRESU='10^3/uL' and .Z<AVAL<75.1, CRIT1FL='Y'; For PARAMCD='WBC' and LBORRESU='10^3/uL' and .Z<AVAL<=2.8, CRIT1FL='Y'	Cond
CRIT2	Analysis Criterion 2	text	100		Derived: For PARAMCD='ALP' and CRIT2FL='Y', CRIT2='Alkaline Phosphatase (U/L) >=3 x ULN'; For PARAMCD='ALT' and CRIT2FL='Y', CRIT2='Alanine Aminotransferase (U/L) >=3 x ULN'; For PARAMCD='AST' and CRIT2FL='Y', CRIT2='Aspartate Aminotransferase (U/L) >=3 x ULN';	Perm

Variable Name	Variable Label	Type	Length/Display Format	Controlled Terms or Format	Source/Derivation/Comment	Core
					For PARAMCD='BICARB' and CRIT2FL='Y', CRIT2='Bicarbonate >=30 mmol/L'; For PARAMCD='BILI' and CRIT2FL='Y', CRIT2='Bilirubin, Total >=2.0 mg/dL'; For PARAMCD='BUN' and CRIT2FL='Y', CRIT2='Blood Urea Nitrogen >30 mg/dL'; For PARAMCD='CA' and CRIT2FL='Y', CRIT2='Calcium >12 mg/dL'; For PARAMCD='CHOL' and CRIT2FL='Y', CRIT2='Cholesterol, Total >300 mg/dL'; For PARAMCD='CL' and CRIT2FL='Y', CRIT2='Chloride >=118 mmol/L'; For PARAMCD='CK' and CRIT2FL='Y', CRIT2='Creatine Kinase (U/L) >3 x ULN'; For PARAMCD='CREAT' and CRIT2FL='Y', CRIT2='Creatinine >=2.0 mg/dL'; For PARAMCD='GGT' and CRIT2FL='Y', CRIT2='Gamma Glutamyl Transferase >=3 x ULN'; For PARAMCD='GLUC' and CRIT2FL='Y', CRIT2='Glucose >200 mg/dL'; For PARAMCD='LDH' and CRIT2FL='Y', CRIT2='Lactate Dehydrogenase (U/L) >3 x ULN'; For PARAMCD='LDL' and CRIT2FL='Y' then CRIT2='LDL Cholesterol >=160 mg/dL'; For PARAMCD='PHOS' and CRIT2FL='Y', CRIT2='Phosphate >5 mg/dL'; For PARAMCD='K' and CRIT2FL='Y', CRIT2='Potassium >5.5 mmol/L'; For PARAMCD='PROLCTN' and CRIT2FL='Y', CRIT2='Prolactin (ng/mL) >1 x ULN'; For PARAMCD='SODIUM' and CRIT2FL='Y', CRIT2='Sodium >150 mmol/L'; For PARAMCD='TRIG' and SEX='F' and CRIT2FL='Y', CRIT2='Triglycerides >=120 mg/dL (Female)'; For PARAMCD='TRIG' and SEX='M' and CRIT2FL='Y', CRIT2='Triglycerides >=160 mg/dL (Male)'; For PARAMCD='TSH' and CRIT2FL='Y', CRIT2='Thyrotropin >5.5 ulU/mL'; For PARAMCD='URATE' and CRIT2FL='Y', CRIT2='Urate >9 mg/dL'; For PARAMCD='EOS' and CRIT2FL='Y', CRIT2='Eosinophils >1x10^3/uL'; For PARAMCD='PLAT' and CRIT2FL='Y', CRIT2='Platelets >=700x10^3/uL'; For PARAMCD='WBC' and CRIT2FL='Y', CRIT2='Leukocytes >=16x10^3/uL'	
CRIT2FL	Analysis Criterion 2 Flag	text	1	NYNULL.NY: (1) Y (2) N	Derived: For PARAMCD='ALP' and LBORRESU='U/L' and AVAL>=3*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='ALT' and LBORRESU='U/L' and AVAL>=3*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='AST' and LBORRESU='U/L' and AVAL>=3*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='BICARB' and LBORRESU='mmol/L' and AVAL>=30, CRIT2FL='Y'; For PARAMCD='BILI' and LBORRESU='mg/dL' and AVAL>=2.0, CRIT2FL='Y'; For PARAMCD='BUN' and LBORRESU='mg/dL' and AVAL>30, CRIT2FL='Y'; For PARAMCD='CA' and LBORRESU='mg/dL' and AVAL>12, CRIT2FL='Y'; For PARAMCD='CHOL' and LBORRESU='mg/dL' and AVAL>300, CRIT2FL='Y'; For PARAMCD='CL' and LBORRESU='mmol/L' and AVAL>118, CRIT2FL='Y'; For PARAMCD='CK' and LBORRESU='U/L' and AVAL>3*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='CREAT' and LBORRESU='mg/dL' and AVAL>=2.0, CRIT2FL='Y'; For PARAMCD='GGT' and LBORRESU='U/L' and AVAL>=3*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='GLUC' and LBORRESU='mg/dL' and AVAL>200, CRIT2FL='Y'; For PARAMCD='LDH' and LBORRESU='U/L' and AVAL>3*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='LDL' and LBORRESU='mg/dL' and AVAL>=160, CRIT2FL='Y'; For PARAMCD='PHOS' and LBORRESU='mg/dL' and AVAL>5, CRIT2FL='Y'; For PARAMCD='K' and LBORRESU='mmol/L' and AVAL>5.5, CRIT2FL='Y'; For PARAMCD='PROLCTN' and LBORRESU='ng/mL' and AVAL>1*ANRHI and ANRHI>.Z, CRIT2FL='Y'; For PARAMCD='SODIUM' and LBORRESU='mmol/L' and AVAL>150, CRIT2FL='Y'; For PARAMCD='TRIG' and LBORRESU='mg/dL' and SEX='F' and AVAL>=120, CRIT2FL='Y' ; For PARAMCD='TRIG' and LBORRESU='mg/dL' and SEX='M' and AVAL>=160, CRIT2FL='Y' ;	Cond

Variable Name	Variable Label	Type	Length/Display Format	Controlled Terms or Format	Source/Derivation/Comment	Core
					For PARAMCD='TSH' and LBORRESU='uIU/mL' and AVAL>5.5, CRIT2FL='Y'; For PARAMCD='URATE' and LBORRESU='mg/dL' and AVAL>9, CRIT2FL='Y'; For PARAMCD='EOS' and LBORRESU='10^3/uL' and AVAL>1, CRIT2FL='Y'; For PARAMCD='PLAT' and LBORRESU='10^3/uL' and AVAL>=700, CRIT2FL='Y'; For PARAMCD='WBC' and LBORRESU='10^3/uL' and AVAL>=16, CRIT2FL='Y'	
CRIT3	Analysis Criterion 3	text	100		Derived: For PARAMCD='URATE' and SEX='F' and CRIT3FL='Y', CRIT3='Urate >8 mg/dL (Female)'; For PARAMCD='URATE' and SEX='M' and CRIT3FL='Y', CRIT3='Urate >10 mg/dL (Male)'	Perm
CRIT3FL	Analysis Criterion 3 Flag	text	1	NYNULL.NY: (1) Y (2) N	Derived: For PARAMCD='URATE' and LBORRESU='mg/dL' and AVAL>8 and SEX='F' CRIT3FL='Y'; For PARAMCD='URATE' and LBORRESU='mg/dL' and AVAL>10 and SEX='M' CRIT3FL='Y'	Cond
ITTR01FL	Intent-To-Treat Record-Level Flag 1	text	1	YNULL.NY: (1) Y	Derived: If PARCAT1 in ('CHEMISTRY','HEMATOLOGY'), 'Y' if the subjects had both non-pcsa baseline and non-missing post-baseline assessment with APHASEN>=1 Note: Only populated for Lab Tests with PCSA criteria CRIT1 defined in SAP	Cond
ITTR02FL	Intent-To-Treat Record-Level Flag 2	text	1	YNULL.NY: (1) Y	Derived: If PARCAT1 in ('CHEMISTRY','HEMATOLOGY'), 'Y' if the subjects had both non-pcsa baseline and non-missing post-baseline assessment with APHASEN>=1 Note: Only populated for Lab Tests with PCSA criteria CRIT2 defined in SAP	Cond
ITTR03FL	Intent-To-Treat Record-Level Flag 3	text	1	YNULL.NY: (1) Y	Derived: If PARCAT1 in ('CHEMISTRY','HEMATOLOGY'), 'Y' if the subjects had both non-pcsa baseline and non-missing post-baseline assessment with APHASEN>=1 Note: Only populated for Lab Tests with PCSA criteria CRIT3 defined in SAP	Cond
ANL01FL	Analysis Record Flag 01	text	1	YNULL.NY: (1) Y	Derived: 'Y' if the record is the first non-missing minimal value among all post-baseline visits including Early Termination visits and unscheduled visits (APHASEN>=1)	Cond
ANL02FL	Analysis Record Flag 02	text	1	YNULL.NY: (1) Y	Derived: 'Y' if the record is the first maximal value among all post-baseline visits and unscheduled visits including Early Termination visits (APHASEN>=1)	Cond