Functional Specifications for Propensity Score Table 1

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I. BACKGROUND & RATIONALE

The Sentinel Propensity Score (PS) adjustment tool enables stratified, 1:1 matched, and variable-ratio matched analyses. In contrast to fixed-ratio matching (e.g., 1:1 propensity score matching), stratification and variable-ratio matching require accounting for the different numbers of patients in each stratum or matched set in order to control for confounding. Baseline covariate characteristics tables (i.e., 'Table 1') among the matched populations are typically used to assess covariate balance as a proxy for confounding control when performing matched analyses. Currently, no such table exists for stratified analyses to enable capture of balance within and across strata in an aggregated overall description of the stratified cohort.

A. PROJECT DETAILS

The objective of this Workgroup is to determine the optimal output display(s) for a baseline covariate characteristics table, i.e., Table 1, for propensity score stratified analyses and to write a detailed functional specification to enhance the tool in a manner that is computationally feasible to run in a distributed data environment.

B. APPROACH

The aggregated descriptive table 1 for a stratified cohort will be based on evaluation of absolute and standardized differences for baseline covariates between compared exposure groups with count (%) and mean (sd) for these covariates within exposure groups. The weighted descriptive Table 1 will be based on evaluation of weighted count (%), mean (sd), absolute and standardized differences. The most appropriate weights will be discussed and decided among Workgroup members.

After obtaining the absolute and standardized differences for each baseline covariate within each stratum, the aggregated descriptive Table 1 will also provide the distribution of these values as range and median (interquartile range) for each covariate across strata observed in the aggregated cohort. This table will also identify which strata provided the minimum and maximum values for absolute and standardized differences. The specification will include an option for producing separate table for each stratum.

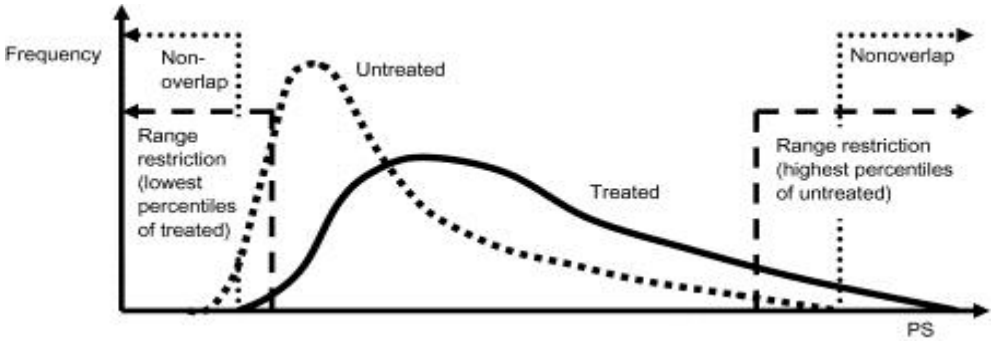
The workgroup will clearly describe in the functional specification the information or data structure – for both the risk-set and patient-level data requests – that will be transferred from the Data Partners, and the additional aggregation process that will be done at the Sentinel Operations Center to produce the final descriptive table. Patient-level data requested by the Sentinel Operations Center and provided by Data Partners must be limited to the minimum amount necessary to accomplish the intended purpose of the request.

II. FLEXIBLE USER SPECIFIED PARAMETERS

Flexible Parameters	Definition	User Specification	Default Option	Example
Trim	% of PS to trim (asymmetrically)	%	Trim only new users outside the area of PS overlap for exposed and comparator	**1%** - after excluding patients in non-overlapping areas, trims both exposed and unexposed patients with PS > the top 1% of the comparators or PS < the bottom 1% of exposed. *See figure below*
N_strata	Number of strata	Integer	50	**100** - creates 100 strata based on percentiles within exposed group, uses same PS cutpoints for comparator group strata.
Estimand	Average treatment effect in treated (ATT) or average treatment effect (ATE)	ATT, ATE	ATT	**ATT** - new users will be weighted to estimate the average treatment effect in the exposed
Tables	Which tables to output	Overall, strata distribution, strata specific*	Overall crude and weighted tables within DP with figure of weighted distribution of absolute and standardized differences across strata	**Strata specific** - creates overall crude and weighted tables within DP with figure of weighted distribution of absolute and standardized differences across strata AND tables with strata specific weighted distribution of baseline characteristics

*Warning: examining balance within strata should be done with caution. Strata with few patients are likely to yield chance imbalances even if the stratification and weigting acheives balance overall across all the strata.

Figure 1. Assymetrical trimming



III. ENHANCEMENTS TO CIDA AND PROPENSITY SCORE

A. TRIM COHORT

After fitting the propensity score, for each patient (row) create variable *trim* = 1 if the estimated PS for that individual is outside the area of common support for the compared groups, otherwise trim = 0. e.g. trim = 1 if comparator PS < minumum PS in exposed or trim = 1 if exposed PS > maximum PS in comparator.

Additionally, change trim to 1 based on user specified trim criteria – e.g. identify the top 1% of PS values in the comparator group and exclude all patients in both groups with larger PS values.

B. IDENTIFY STRATA

In the cohort that remains after trimming (i.e., the "trimmed cohort"), identify strata based on percentiles calculated in the exposed group (where the number of strata is a user defined option). Use the same PS boundaries for the strata identified in the exposed group to assign strata for the comparator group.

C. CREATE WEIGHTS

For the trimmed cohort, create variables *weight_ATT* and *weight_ATE* using the following formulas:

ATT weights (note: unexposed = comparator)	**ATE weights** (note: unexposed = comparator)
Exposed = 1	Exposed = $\frac{(N_{\text{Total in strata i}}/N_{\text{Total}})}{(N_{\text{exposed in strata i}}/N_{\text{total exposed}})}$
Comparator = $\frac{(N_{\text{exposed in strata i}}/N_{\text{total exposed}})}{(N_{\text{unexposed in strata i}}/N_{\text{total unexposed}})}$	Comparator = $\frac{(N_{\text{Total in strata i}}/N_{\text{Total}})}{(N_{\text{unexposed in strata i}}/N_{\text{total unexposed}})}$

D. WEIGHTED STRATIFIED ANALYSES

1. For protocols where individual level data are returned to the SOC

Fit a Cox model in trimmed data with a weight statement where weight = *weight_ATT* or *weight_ATE* depending on user selected estimand of interest.

The weighted analysis should use robust standard errors.

```
proc phreg data=trimmed_individual covs;
weight weight_att;
model Time*Status(0)= exposure;
run;
```

* robust standard errors;
* weight statement;

The crude analysis remains an unweighted Cox model in the untrimmed cohort with usual standard errors.

```
proc phreg data= untrimmed_individual;
model Time*Status(0)= exposure; run;
```

2. For protcols where risk set level data is returned to the SOC

Fit a Cox regression model in trimmed data using counting process syntax by expanding cell counts, mean and variance of weights for user selected estimand of interest (ATE/ATT) to recreate an individual level dataset. (see example macro provided by Bruce Fireman)

```
proc phreg data=trimmed_riskset covs;
weight weight_att;
model (start,stop) * event(0) = exposed /risklimits ties=efron;
run;
```

The crude analysis remains an unweighted Cox model using counting process syntax by expanding cell counts to recreate an individual level dataset. (see example macro provided by Bruce Fireman)

```
proc phreg data=untrimmed_riskset covs;
model (start,stop) * event(0) = exposed /risklimits ties=efron;
run;
```

* robust standard errors;
* weight statement;
* start = risk set # - 0.1, stop = risk set #

IV. AGGREGATION ACROSS DATA PARTNERS

A. RISK SETS

If the risk set rather than the individual level data option is selected, two datasets containing risk set information should be returned to SOC:

Risk sets are anchored to outcome occurrence and are defined at the time that each outcome occurs.

1. Risk sets for the untrimmed cohort
2. Risk sets for the trimmed cohort (with relevant ATT or ATE weights)

Risk set level data must include cell counts, mean and variance of weights for 1) exposed cases, 2) comparator cases, 3) exposed non-cases, 4) comparator non-cases *for each risk set*

Example for one risk set in a cohort:

Exposure	Outcome	Count	Weight_mean	Weight_variance
1	1	20	5	1.5
1	0	230	6	0.8
0	1	10	4	1.2
0	0	240	5	6

B. TABLE 1 ACROSS DATA PARTNERS

Binary characteristics can be aggregated by summing weighted counts and deriving %.

- Absolute and standardized differences calculated as usual

Continuous characteristics can be aggregated by taking a weighted average.

- Absolute differences calculated as usual, standardized difference calculated with pooled standard deviation

V. EXAMPLE TABLE SHELLS

A. DATA PARTNER SPECIFIC TABLES (CRUDE AND PROPENSITY STRATA WEIGHTED)

1. Table 1 Overall Baseline Characteristics

Crude

	Exposed	**Comparator**		
	N (%)	N (%)	Abs Diff	Std Diff
Female	8208 (35.99)	22228 (39.37)	-3.38	-0.70
Hypertension	22058 (96.72)	53871 (95.42)	1.30	0.07
Diabetes	4773 (20.93)	14242 (25.23)	-4.30	-0.10
	Mean (sd)	Mean (sd)	Abs	
Age	67.29 (12.22)	71.10 (12.13)	-3.81	-0.31
Number of generics	11.41 (6.18)	12.15 (6.58)	-0.74	-0.12

Propensity Score Strata Weighted

	Exposed	**Comparator**		
	N (%)	N (%)	Abs Diff	Std Diff
Female	8208 (35.99)	20319.47 (35.99)	0.00	0.00
Hypertension	22058 (96.72)	54686.78 (96.87)	-0.15	-0.01
Diabetes	4773 (20.93)	11722.85 (20.77)	0.16	0.00
	Mean (sd)	Mean (sd)	Abs	
Age	67.29 (12.22)	66.73 (12.59)	0.57	0.05
Number of generics	11.41 (6.18)	11.55 (6.25)	-0.14	-0.03

B. AGGREGATED DATA PARTNER TABLES (CRUDE AND PROPENSITY STRATA WEIGHTED)

1. Table 1 Overall Baseline Characteristics

Crude

	Exposed	**Comparator**		
	N (%)	N (%)	Abs Diff	Std Diff
Female				
Hypertension				
Diabetes				
	Mean (sd)	Mean (sd)	Abs	
Age				
Number of generics				

Propensity Score Strata Weighted

	Exposed	**Comparator**		
	N (%)	N (%)	Abs Diff	Std Diff
Female				
Hypertension				
Diabetes				
	Mean (sd)	Mean (sd)	Abs	
Age				
Number of generics				

2. Table 2 Covariate Balance Distribution Across Weighted Strata

	Abs Diff (exposure A – exposure B) median (IQR)	Range	Std Diff (exposure A – exposure B) median (IQR)	Range	MinAbs	MaxAbs	MinStd	MaxStd
Female	0.43 (5.31)	(-7.39, 9.06)	0.01 (0.11)	(-0.17, 0.18)	Stratum 49	Stratum 27	Stratum 49	Stratum 27
Hypertension	-0.06 (1.38)	(-4.24, 7.41)	0.00 (0.08)	(-0.18, 0.33)	Stratum 4	Stratum 1	Stratum 8	Stratum 1
Diabetes	0.63 (4.19)	(-6.73, 13.20)	0.02 (0.11)	(-0.16, 0.28)	Stratum 7	Stratum 27	Stratum 7	Stratum 27
Age	0.62 (1.06)	(-4.15, 2.29)	0.07 (-0.11)	(-0.61, 0.24)	Stratum 6	Stratum 10	Stratum 6	Stratum 10
Number of generics	0.40 (1.06)	(-1.59, 2.54)	0.07 (0.17)	(-0.15, 0.44)	Stratum 49	Stratum 5	Stratum 49	Stratum 5

Identify most extreme strata

3. Table 3 Baseline Characteristiscs within Weighted Strata

Strata 1

	Exposed	Comparator		
	N (%)	N (%)	Abs Diff	Std Diff
Female	28 (49.12)	58.45 (41.43)	7.70	0.16
Hypertension	56 (98.25)	128.17 (90.84)	7.41	0.33
Diabetes	20 (35.09)	48.02 (34.03)	1.06	0.02
	Mean (sd)	Mean (sd)	Abs	
Age	67.50 (11.27)	69.58 (3.76)	-2.08	-0.25
Number of generics	15.68 (8.38)	15.10 (2.41)	0.59	0.09

Strata 2

	Exposed	Comparator		
	N (%)	N (%)	Abs Diff	Std Diff
Female	22 (47.83)	45.43 (39.90)	7.93	0.16
Hypertension	42 (91.30)	103.36 (90.77)	0.53	0.02
Diabetes	20 (43.48)	34.48 (30.28)	13.2	0.28
	Mean (sd)	Mean (sd)	Abs	
Age	71.25 (11.45)	71.45 (3.38)	-0.20	-0.02
Number of generics	15.96 (8.22)	13.65 (2.02)	2.31	0.39

Figure 2. Covariate balance distribution across weighted strata

Box plot of covariate balance distribution across weighted strata for each covariate