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Practical Process in SAS of Using External Controls

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ABSTRACT

Usage of real-world data (RWD) or historical data as external controls (EC) for assessing treatment effect in rare disease or early oncology drug development are increasingly accepted by regulatory agencies. Various methods have been developed to construct external control arm for single-arm trial or supplement control arm in the current trial. In this paper, we present practical implementations in SAS® for the process to generate well-matched EC along with analytic methods in different settings, as well as relevant SAS codes and summary outputs.

INTRODUCTION

Using External control is particularly useful when it's challenging to recruit enough participants from a limited population or ethically problematic to have a placebo-controlled group[1]. In single-arm trials, external controls can serve as a comparison group to provide evidence of treatment effectiveness safety. Augmenting the concurrent control arm with external controls in the randomized controlled trial can increase the power of the study to detect the treatment effect. Patient-level data from historical clinical trials or real-world data such as natural history studies can be the potential sources of external controls. Selection of the suitable data sources, eligibility criteria and definition of time 0 for external control need rigorous consideration, which are not the focus of this paper.

Proper statistical methods to use the selected external data sources are crucial to minimize bias and ensure statistical balancing of baseline characteristics and the reliability of the trial outcomes. Propensity score (PS) methods are wildly utilized to estimate treatment effects in observational research. A propensity score is the conditional probability of being assigned to a treatment group, given the observed baseline characteristics. Propensity scores are used to identify control subjects who are similar to those in the current trial. Methods like PS matching, PS Weighting, Weighting after matching are often applied for single-arm trials, and a Test-then-Pool approach for supplemental concurrent control to estimate the treatment effect. In this paper, we will present our sample code along with an example dataset provided in Table 1.

Variable Name	Description	Type/Code/Value
STUDYID	Study Identifier	Character
USUBJID	Unique Subject Identifier	Character
TRTPN	Treatment group number	0 = External Control 1 = Active Drug 2 = Concurrent Control
BAGEGR	Baseline Age Group	Categorical
BVAR1	Baseline Covariate 1	Continuous
BVAR2	Baseline Covariate 2	Continuous
BVAR3	Baseline Covariate 3	Continuous
AVISITN	Analysis Visit	1 = Baseline 2 = Visit 1
AVAL	Analysis Value	Continuous
BASE	Baseline Value	Continuous
CHG	Change from Baseline	Continuous

Table 1. Example dataset used as input for the sample code below.

PROPENSITY SCORE METHODS

Propensity score calculation and matching and/or weighting will be used to achieve baseline profile balance between active drug treated subjects and the EC subjects.
Propensity scores are estimated by logistic regression model:

- Response variable: if a subject was treated by active drug (trtpn=1) or in EC studies (trtpn=0).
- Independent variables: baseline characteristics

```
proc logistic data=indata desc;
  where trtpn in (0,1);
  model trtpn = bvar1 bvar2 bvar3 / link=logit rsquare ;
  output out=ps_los pred=ps xbeta=logit_ps;
run;
```

This code is used to calculate propensity scores and their logit-transformed values based on a logistic regression model. It filters the dataset to include only records with trtpn values of 0 and 1, uses predictor variables (bvar1, bvar2, bvar3), and outputs the results in a dataset named ps_los. The desc option indicates that the response variable (trtpn) is treated in descending order. The link=logit option indicates that the logistic regression is using the logit link function, which is standard for binary outcomes. The rsquare option requests R-square statistics for the model, which provides a measure of goodness-of-fit. The output statement creates an output dataset named ps_los. The predicted probabilities (propensity scores) are stored in the new variable ps. The logit-transformed predicted values (linear predictor values) are stored in the new variable logit_ps.

PROPENSITY SCORE MATCHING

- Exact matched - optimal method with caliper =0.25

```
proc psmatch data=indata region=allobs;
  class trtp;
  psmodel trtp(treated='xxx')= bvar1 bvar2 bvar3;
  match method =greedy (k=6) caliper =0.25;
  output out(obs=all)=outps matchid=_matchid;
run;
```

This code matches treated and untreated subjects based on their propensity scores using a greedy algorithm and a caliper of 0.25 for better precision in the matches. The output dataset (outps) contains matched pairs along with their unique match IDs for further analysis

- Group matched EC subjects with PS in the range of treated subjects will be included in the analyses as matched EC subjects.

```
proc psmatch data=indata region=treated(EXTEND=0);
  class trtp;
  psmodel trtp(treated='xxx')= bvar1 bvar2 bvar3;
  output out(obs=region)=outps;
run;
```

This code calculates propensity scores based on the specified model and limits the analysis region to treated observations. The matched data is saved in the dataset outps, which includes only observations in the analysis region.

PROPENSITY SCORE WEIGHTING

The average treatment effect for the treated (ATT) weight will be calculated for each subject. Specifically, the randomized subjects (active drug treated or concurrent control subjects) will have a weight of 1, and the EC subjects will have a weight of PS / (1-PS), where PS is the propensity score. The ATT weight can also obtained through PROC PSMATCH.

```
proc psmatch data=indata region=allobs;
  class trtp;
  psmodel trtp(treated='xxx')= bvar1 bvar2 bvar3;
  output out(obs=region)=outps; * still can get ATT weight;
run;

data pswt;
  set ps_los;
  if trtp='EC' then attwgt = _ps_/(1-_ps_);
  else              attwgt = 1;
run;
```

TEST-AND-POOL

The Test step ensures that External Control (EC) is comparable to Concurrent Control (CC) in terms of both baseline characteristics and efficacy outcome. A Test-and-Pool data approach is implemented[2], involves an initial step of identifying relevant controls through propensity score matching methods. Following this, a statistical test is conducted to compare outcome variables between the EC and the CC. If the test identifies significant differences, pooling is not performed. Otherwise, EC and CC can pool to increase the statistics power.

EFFICACY OUTCOME SIMILARITY ASSESSMENT

- weighted ANCOVA model to obtain estimates

```
proc glm data = indata ;
  class trtp bagegr;  /* trtp includes 3 levels */
  model chg =  trtp bvar1 bvar2 bvar3 / solution ;
  weight attwgt;
  lsmeans trtp / cl diff stderr;
  ods output lsmeans = theta;
run;
```

- Test-and-Pool assessment

```
data theta1;
  set theta(where=(trtp='Concurrent Control')
      rename=(lsmean=theta_cc stderr=se_theta_cc));
  set theta(where=(trtp='External Control')
      rename=(lsmean=theta_ec stderr=se_theta_ec));
  abs_diff = abs(theta_cc - theta_ec);
  t_cc = 1/(se_theta_cc ** 2);
  t_ec = 1/(se_theta_ec ** 2);
  crit_value = quantile('NORMAL', 1 - &gamma/2);
  se = sqrt(1/t_ec + 1/t_cc);
  criteria = crit_value * se;
  gamma = &gamma;
  z_test = abs_diff / se ;
  p_value = 2 * (1 - CDF('NORMAL', z_test));
  significant = (abs_diff < criteria);
  if significant=1 then pooled = 'Yes';
  else                  pooled = 'No';
run;
```

POOL

If the data from EC are comparable with CC, the estimated treatment effect (active drug versus the combined control CC + EC) will be obtained from the ATT weighted ANCOVA model.

- Response variable: change in efficacy outcome.
- Independent variables: treatment group and baseline covariates

Based on the weighted ANCOVA model, the least square mean (LSMean) estimates of mean change for each treatment group, the difference of LSM estimates between treatment group, and their corresponding standardized error and 95% confidence intervals will be calculated.

BASELINE CHARACTERISTICS BALANCE ASSESSMENT

The balance of baseline characteristics[3] between the ATT weighted randomized group and the EC group will be evaluated by examining the standardized mean difference in baseline functional endpoints involved in the calculation of propensity scores, both before and after the application of propensity score weighting. For reasonable baseline balance, the absolute standardized mean difference should be less or equal to 0.25.
Standardized mean difference is calculated as:

$$d_{(all)} = \frac{mean_1 - mean_2}{S_{(all)}}, \text{ where } S_{(all)} = \sqrt{\frac{variance_1 + variance_2}{2}}$$

- Matching and weighting: S(all) calculation on weighted
- Weighting (all obs): S(all) all obs

CONCLUSION

The use of real-world data as external controls is becoming increasingly recognized as a valuable approach in clinical trials. Implementing external controls requires meticulous selection of data sources and application of proper statistical methods to ensure reliable and unbiased results. Propensity score methods, including matching and weighting techniques, are widely applied to achieve balance between treatment groups and minimize bias. The Test-and-Pool method enable the integration of external controls with randomized controlled trials.

This paper has demonstrated practical examples of constructing external controls using SAS, providing detailed code to illustrate these processes in various trial settings. By leveraging external controls, researchers can optimize trial designs and improve the generation of evidence, paving the way for more efficient and ethical advancements in drug development.

REFERENCES

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2. Liu Y, Lu B, Foster R, et al. Matching design for augmenting the control arm of a randomized controlled trial using real-world data. J Biopharm Stat. 2022;32:124.
3. Austin, PC, Stuart EA. (2015). Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med, 34(28):3661-79.

CONTACT INFORMATION

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