

Mitigating study power loss in disrupted clinical trials: Leveraging external data via the propensity score-integrated approach

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Outline

• A novel statistical procedure for leveraging external data in medical product evaluation

- Today's focus: Propensity score-integrated approach

- Application: mitigating study power loss for a clinical study cut short due to the COVID-19 pandemic (this study will be called the "current study" henceforth)
- Concluding remarks

Basic Statistical Ingredients

• Power prior (Bayesian)

- Borrow external subjects with discounting
- Composite likelihood (frequentist)
 - Incorporate external subjects with down-weighting
- Propensity score methodology
 - Balance subject characteristics (covariates) between two groups: current study subjects and external subjects
- Propensity score-integrated approach Today's focus
 - Propensity score-integrated power prior Bayesian
 - Propensity score-integrated composite likelihood Frequentist
 - Goal: the augmentation of the current study with external data while maintaining study integrity

Bayesian Power Prior

• A power prior is constructed as

$$\pi(\theta/D_0, \alpha) \propto [L(\theta/D_0)]^{\alpha} \pi_0(\theta)$$

- θ : parameter of interest
- $L(\theta/D_0)$: likelihood of the external data
- $\pi_0(\theta)$: initial prior distribution for θ
- α : power prior parameter, $0 \le \alpha \le 1$
- α : control how much external data to leverage
 - $\alpha = 0$: no leverage
 - $\alpha = 1$: full leverage
- Question: how and when to determine α for a prospective investigational study?

Ref. Chen, M-H and Ibrahim, J.G., (2000) Power Prior Distribution for Regression Models. Statistical Science, 15(1): 46-60

Composite Likelihood



• General form (weighted product of probability density functions):

$$L(\theta|Y) = \prod_{i} f(y_i |\theta)^{\lambda_i}$$

where λ_i is nonnegative weight to be chosen, and can be used to discount subject info from external data source.

- We set:
 - $\lambda_i = 1$, if the subject *i* is from the investigational study
 - $0 < \lambda_i \leq 1$, if the subject *i* is from the external data source
 - E.g. If $\lambda_i = 0.6$, 60% of this subject's info is leveraged and 40% discounted.
- Question: how and when to determine λ for a prospective investigational study?
- Ref. Lindsay, BG (1988). Composite likelihood method. *Contemporary mathematics*, 80(1): 221-239. Varin et al (2011). An overview of composite likelihood methods. *Statistica Sinica*, P5-42.

Propensity Score Methodology

- A ground-breaking statistical innovation for the *design* and *analysis* of observational studies, developed by Rosenbaum and Rubin in 1983 (Rosenbaum and Rubin, 1983).
- Propensity score (PS): Conditional probability of receiving treatment A rather than treatment B, given a collection of observed baseline covariates.
- Replace a (large) number of observed confounding covariates with <u>one</u> <u>scalar function</u> of these covariates: the propensity score.
- Goal in observational studies: Simultaneously balance many observed covariates between the two treatment groups, and then reduce bias in treatment comparison on outcomes.
- Our Goal: Simultaneously balance many observed covariates between the external subjects as one group and current study subjects as the other group, to make leveraging external subjects more justified



Propensity Score Methods

- Propensity score is estimated through statistical modeling of relationship between the covariates and membership of the groups between which covariates are to be balanced.
- Commonly used PS methods in the regulatory settings:
 - Matching on propensity scores

- Stratification on propensity scores
- Weighting using propensity scores
- All these methods can separate study *design* from outcome *analysis*.
- In our application, propensity score stratification is used, propensity scores are estimated by independent statistician blinded to outcome data

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Propensity Score-Integrated Approach

- A new methodology for leveraging external data to augment a prospective investigational study.
 - PS-integrated power prior (PS + PP) Bayesian
 - PS-integrated composite likelihood (PS + CL) Frequentist
- Used to
 - augment a single-arm investigational study with external data,
 - augment one or both arms of an RCT,
 - with the option of discounting/down-weighting information from external data.
- PS -> Study design
- PP or CL -> Outcome analysis



PS-Integrated Approach – Study Design

- Define PS as the conditional probability of being in the current study vs external source, given subject baseline covariates.
- Use PS to design the study:

- Select comparable subjects from external data source
- Stratify the pooled current study and external subjects
- Specify the amount by which information of external subjects is discounted/down-weighted (i.e., determine α in PP or λ in CL)
- Only baseline covariates are used in the above: Outcome free!

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Leveraging External Data -- Caveats

- It is critical to assess whether leveraging external data fits for purpose for the specific objectives of the current study.
- Sufficient external data quality and integrity are essential for regulatory decision-making *relevance and reliability*.
- Outcome-free planning is critical *trial integrity and transparency*.
- Early consultation with relevant FDA review division is important (FDA guidance documents).
- The propensity score-integrated approach can be used
 - To augment single-arm study with external data
 - To augment one or both arms of RCT with external data

A Illustrative Example



- A single-arm clinical study
- Primary endpoint: one-year adverse event
- Parameter of interest: θ, probability of a subject experiencing adverse event(s) within the first year.
- Associated hypothesis testing:

 $H_0: \theta \ge 36\%$ vs: $H_a: \theta < 36\%$

- Sample size determination
 - Assume $\theta = 0.30$
 - Set: power = 80%; significance level = 0.05
 - Then, N = 380

A Illustrative Example (cont.)

- The enrolment was stopped at 290 due to the pandemic, and that it is not practical to reopen the enrolment at a later time.
- It was proposed to
 - borrow 90 = 380 290 subjects from a registry for this device in Europe (the device was approved in EU), using the PS-integrated approaches.
 - identify an independent statistician who was blinded to the outcomes data.
- Based on the subject inclusion/exclusion criteria specified in the current study, 941 subjects were selected from the registry.
- With the covariate data of 1,231 (290 + 941) subjects from the current study and registry, a propensity score model was created by the independent statistician, using logistic regression.
- Propensity score is defined as the probability of a subjects being in the current study instead of the registry conditional on all the covariates.

 Table 1. Sample Sizes in PS Stratum



	1	2	3	4	5	Total
Current Study (n)	58	58	58	58	58	290
Registry (n)	281	210	154	187	109	941

- Five PS strata were formed, and balance for each covariate was checked using numerical and graphical methods.
- Note:
 - 90 external subjects were to be leveraged, but 941 identified.
 - Only partial info from each of 941 external subjects could be leveraged.
 - Partial? How much? Depending on what?
- Step 1 Split 90 nominal subjects into 5 PS strata
- Step 2 Determine power parameter α or exponent λ within each stratum



Step 1. Split 90 nominal subjects

- Split 90 nominal subjects into 5 PS strata, *proportional* to the similarity of external and the current subjects in terms of baseline covariates.
- The similarity is measured by an *overlapping coefficient*, the overlapping area of propensity score distributions of the two groups of subjects.



Overlapping Coefficients

PS Stratum						
	1	2	3	4	5	Total
Current Study (n)	58	58	58	58	58	290
Current Study (n) Registry (n) Overlap Coeff	281	210	154	187	109	941
Overlap Coeff	0.87	0.78	0.86	0.84	0.77	



Standardized Overlapping Coefficients

PS Stratum						
	1	2	3	4	5	Total
Current Study (n)	58	58	58	58	58	290
Registry (n)	281	210	154	187	109	941
Overlap Coeff	0.87	0.78	0.86	0.84	0.77	
Current Study (n) Registry (n) Overlap Coeff Std. Overlap Coef.	21%	19%	21%	20%	19%	100%



Splitting 90 Nominal External subjects

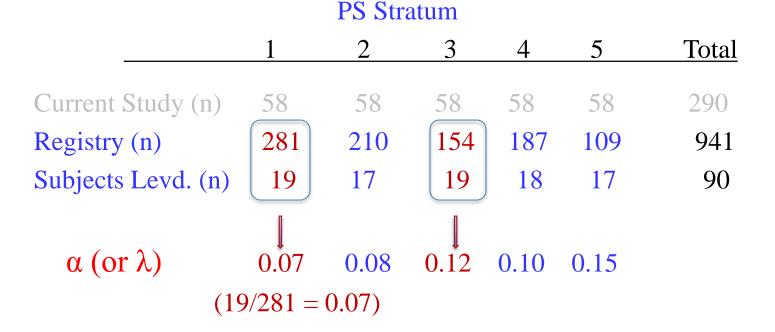
PS Stratum							
	1	2	3	4	5	Total	
Current Study (n)	58	58	58	58	58	290	
Registry (n)	281	210	154	187	109	941	
Overlap Coeff	0.87	0.78	0.86	0.84	0.77		
Std. Overlap Coef.	21%	19%	21%	20%	19%	100%	
Subjects Leveraged	19	17	19	18	17	90	
$(90 \text{ x } 21\% = 19) \qquad (90 \text{ x } 19\% = 17)$						= 17)	

• The number of external subjects allocated to each PS stratum is proportional to their *standardized overlapping coefficient*.



Step 2. Determining How Much Info to Leverage

- The info leveraged from each individual external subject depends on how many external subjects in that PS stratum.
- The power prior parameter for each individual external subject, α , is inversely proportional to the sample size of external subjects in the PS stratum.



Leveraging External Data Planning – Finished



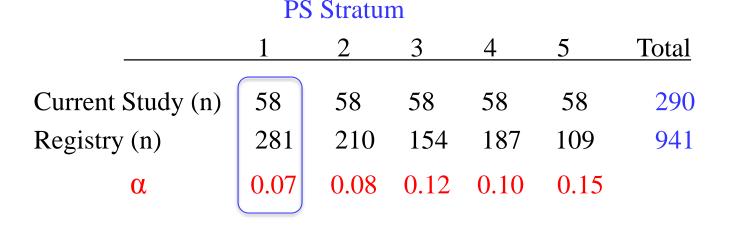
• We know

- The PS stratum each subject would belong to.
- How much info each external subject could contribute.
- Study operating characteristics: 80% power; 5% Type I error rate.

PS Stratum						
	1	2	3	4	5	Total
Current Study (n)	58	58	58	58	58	290
Registry (n)	281	210	154	187	109	941
α (or λ)	0.07	0.08	0.12	0.10	0.15	

Outcome Analysis (Power Prior)

• After the clinical outcome was observed from all the subjects, the final analysis was conducted, based on the PS study design:



- Apply the power prior approach within each stratum to get stratumspecific posterior distribution, which are then combined to complete the inference for the parameter of interest.
- The posterior probability of $\theta < 36\%$ is 96.9%, which meets the study success criterion.

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Outcome Analysis (Composite Likelihood)

• After the clinical outcome was observed from all the subjects, the final analysis was conducted.

PS Stratum						
	1	2	3	4	5	Total
Current Study (n)	58	58	58	58	58	290
Current Study (n) Registry (n)	281	210	154	187	109	941
λ	0.07	0.08	0.12	0.10	0.15	

- Apply the composite likelihood approach to get stratum-specific parameter estimates, which are then combined to complete the inference for the parameter of interest.
- Maximum likelihood estimate of $\theta = 31\%$, *p*-value = 0.01.

Concluding Remarks

- Novel statistical methods play a critical role in leveraging external data to support regulatory decisions.
- Propensity score-integrated approaches can be applied to incorporate external data for a prospective investigational clinical study.
- Propensity score-integrated approach can be utilized to mitigate study power loss due to the COVID-19 pandemic.



US FDA Guidance

- US Food and Drug Administration (2020), "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency," available at <u>https://www.fda.gov/regulatory-</u> information/search-fda-guidance-documents/fda-guidance-conductclinical-trials-medical-products-during-covid-19-public-healthemergency.
- US Food and Drug Administration (2020), "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry," available at <u>https://www.fda.gov/regulatory-</u> information/search-fda-guidance-documents/statistical-considerationsclinical-trials-during-covid-19-public-health-emergency-guidanceindustry.



PS-Integrated Approaches - Reference

- Wang, C., Li, H., Chen, W., Lu, N., Tiwari, R., Xu, Y., Yue, L. (2019). Propensity Score-Integrated Power Prior Approach for Incorporating Real-World Evidence in Single-Arm Clinical Studies. *Journal of Biopharmaceutical Statistics*, 29 (5),731-748.
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Thank You!