Mitigating Study Power Loss in Clinical Studies Disrupted Due to the COVID-19 Pandemic: Leveraging External Data via Propensity Score-Integrated Approaches

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Abstract

The spread of COVID-19 has created tremendous challenges to ongoing clinical studies essential to finding safe and effective treatments for a myriad of diseases, with some studies having suspended enrollment altogether. This presentation focuses on the recovery of lost study power caused by clinical trial disruptions due to the pandemic.[1] It features an innovative use of the recently developed novel propensity score-integrated Bayesian and Frequentist approaches which may be applicable in cases where studies nearing enrollment completion had to cease enrollment and restarting is not feasible. Through integrating external patients with data already collected, the loss of study power due to the premature stopping could be mitigated. An illustrative example is provided to demonstrate how to implement these methods while preserving study integrity.

Method (Outcome-Free Design)

- Nominal number of external patients to be leveraged (N) = originally planned sample size minus the actual number of patients prospectively enrolled at the time the study is stopped.
- Estimate propensity score using patients prospectively enrolled in the disrupted study as one group and external patients as the other group.
- Use estimated propensity score to exclude external patients that are dissimilar with the patients in the disrupted study in terms of baseline covariates.
- Use estimated propensity score to stratify all the patients (disrupted study and external).
- Use estimated propensity score to allocate N among propensity score strata and then determine the amount by which external patients are discounted/down-weighted in each stratum.
- Outcome Analysis: Use *Power Prior*[2] or *Composite Likelihood*[3] for statistical inference.

Step by Step

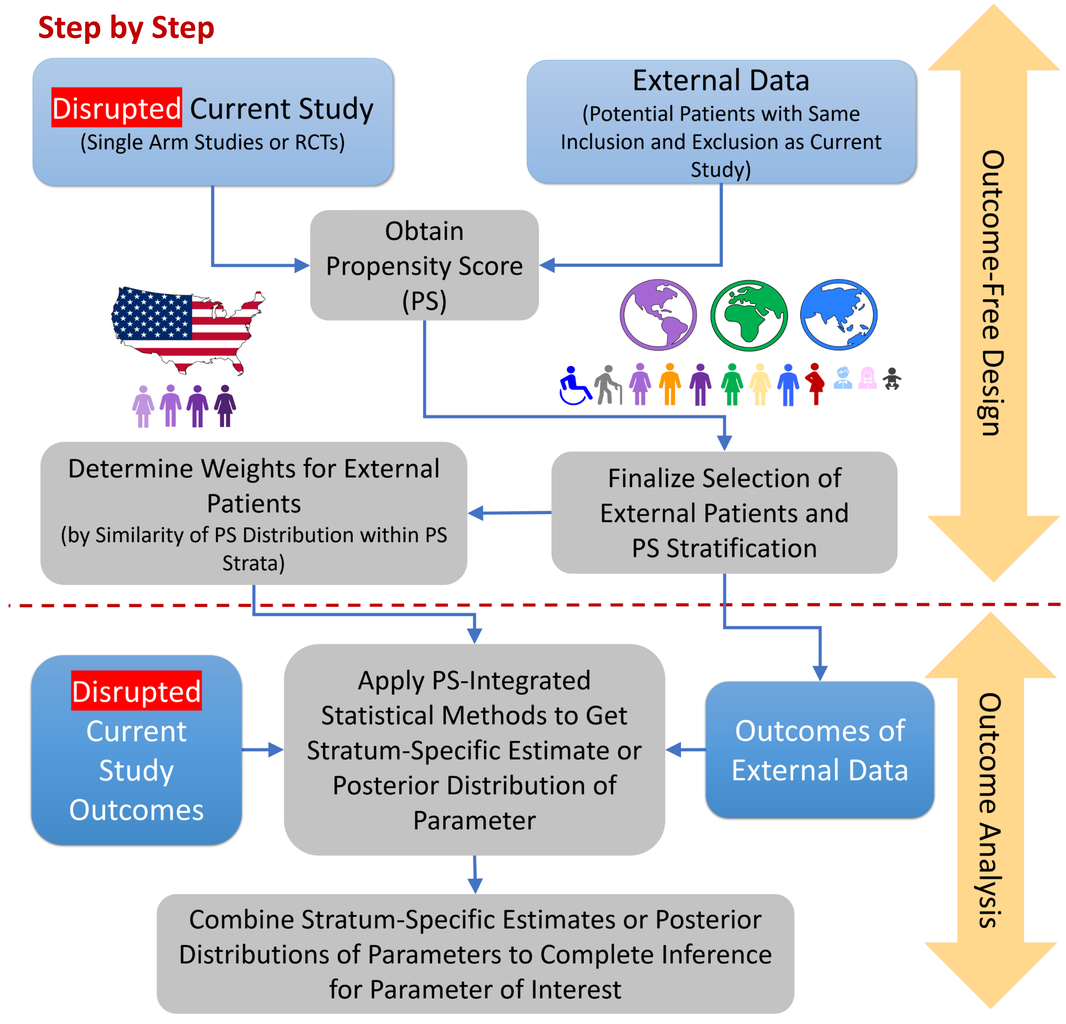

Table 1: Number of patients (disrupted current study, external data, and nominal borrowed) and weights in each PS stratum.

PS Stratum	1	2	3	4	5	Total
Disrupted Current Study (n)	58	58	58	58	58	290
External Data (n)	281	210	154	187	109	941
Nominal Borrowed (N)	19	17	19	18	17	90
Down-Weighting External Data[1-3]	0.07	0.08	0.12	0.10	0.15	

Example

Table 1 is an example of a disrupted single-arm study augmented with external data:

- Original sample size: 380 patients.
- Enrollment disrupted at 290 patients by COVID-19 pandemic.
- Identify 941 external patients.
- Borrow 90 nominal patients (N = 380 - 290).
- Discounting the external patients by power prior or composite likelihood.

Extension to a disrupted two-arm randomized controlled trial: Apply the proposed methodology independently to each arm as if each were a single arm study.

Conclusion

The proposed methodology can be used to leverage external data to augment prospectively designed clinical studies, thereby mitigating power loss in studies disrupted due to the COVID-19 pandemic.

Reference

[1] Li, H., Chen, W.-C., Lu, N., Song, C., Wang, C., Tiwari, R., Xu, Y., and Yue, L. (2021), "Mitigating Study Power Loss Caused by Clinical Trial Disruptions Due to the COVID-19 Pandemic: Leveraging External Data via Propensity Score-Integrated Approaches," Statistics in Biopharmaceutical Research. (DOI:10.1080/19466315.2020.1860813).

[2] Wang, C., Li, H., Chen, W.-C., 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.

[3] Wang, C., Lu, N., Chen, W.-C., Li, H., Tiwari, R., Xu, Y., Yue, L., Propensity Score-Integrated Composite Likelihood Approach for Incorporating Real-World Evidence in Single-Arm Clinical Studies. *Journal of Biopharmaceutical Statistics*, **30**(3), 495—507.