A Two-Stage Study Design Framework for Utilizing External Data to Augment a Clinical Trial

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Randomized Controlled Trials

- Double-masked, randomized, controlled trials (RCTs) are the "gold standard" for clinical outcome studies
- Randomization stochastically balances all covariates, both observed and unobserved

The Need for External Data

- Clinical trial cost (money/time) rising significantly, placing ever-increasing burdens on the medical product development ecosystem
- The 21st Century Cures Act, passed in 2016, placing additional focus on the use of external data to support regulatory decision making of medical products

Sources of External Data

- Prior clinical studies
- Registries
- OUS pre- and post- market studies
- ….

Utilizing External Data to Augment the Control Group

- Prior clinical studies:
- Registries:
- Post- market studies:

Using External Data: Challenges(1)

Data Dredging:

- In selection of external data source/subject
- In data analysis
- Detrimental to regulatory/health care decision making

Using External Data: Challenges(2)

Selection Bias:

- Imbalance in baseline covariates for group comparison (confounding)

Using External Data: Challenges(3)

Other potential sources of bias:

- Temporal, Regional
- Measurement, Evaluation
- Conduct

Maintaining Objectivity in Using External Data

- **Maintaining objectivity is critical to regulatory/health care decision making**
- **Have an Objective Study Design (OSD):** Prospective study design before/without access to outcome data (Separation of study design and analysis)

OSD: a Two-Stage Design Framework

1st Stage (planning)

Population of interest, primary endpoints, sample size, **sources of external data**, quality plan for reduction of **selection bias**

2nd Stage (implementation)

With **no** access to clinical outcome data, study design to reduce selection bias

1st Stage Study Design (1)

Important Points to consider:

- External data fit for use/purpose?
- Quality of the external data
- Implementation plan for selecting subjects and balancing covariates between groups

1st Stage Study Design (2)

Important Points to consider:

- Designating an independent statistician to perform the 2nd Stage Study Design

1st Stage Study Design (3)

Important Points to consider:

- Data source/subject selection criterion cannot be based on any clinical outcome information

2nd Stage Study Design (1)

The Independent Statistician:

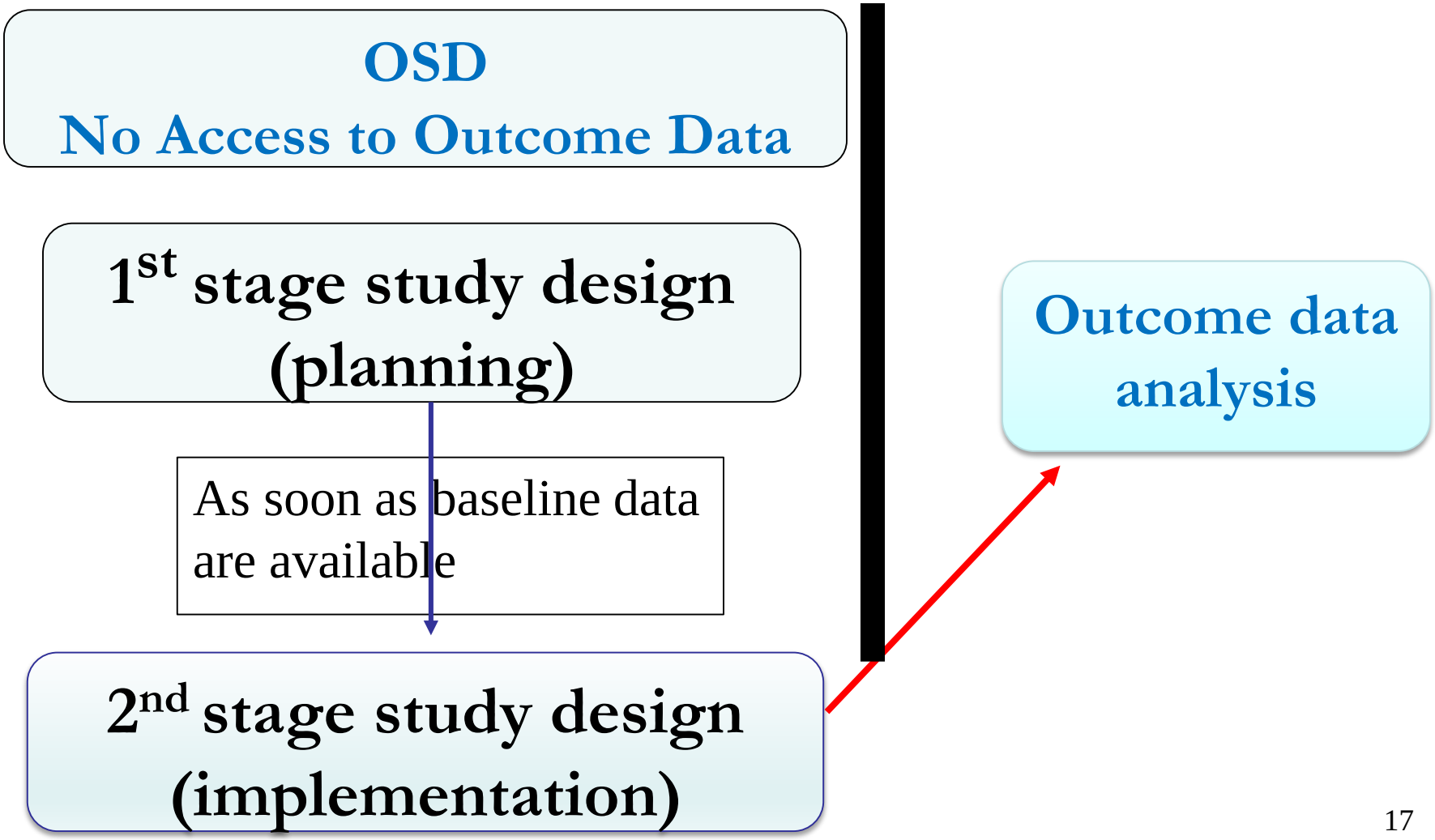
- Select subjects from the external data by the pre-specified procedure/criteria in an outcome free manner
- Perform the study design to balance baseline covariates between groups in an outcome free manner

2nd Stage Study Design (2)

Don't access and analyze the clinical outcome data Until:

- The independent statistician communicates the Design to the sponsor, and the Agency, AND all stakeholders have agreed on the Design

Two-Stage Study Design Framework



An Example

Chen WC, Wang C, Lu N, Li H, Tiwari R, Xu Y, Yue L. (2020)

Propensity Score-Integrated Composite Likelihood Approach for Augmenting the Control Arm of a Randomized Controlled Trial by Incorporating Real-World Data *Journal of Biopharmaceutical Statistics*. 30(3):508-520 https://doi.org/10.1080/10543406.2020.1730877

The Example

- Randomized controlled, a transcatheter aortic valve replacement (TAVR) device vs. surgical repair (Con)
- Using surgical repair data from a registry to augment the control group [**External**]
- Primary endpoint: proportion of subjects died (CV-related) or hospitalized (CV-related) within 12 months after the procedure

1st Stage Design (1)

- Primary endpoint: proportion of subjects died (CV-related) or hospitalized (CV-related) at 12 months after the procedure, superiority
- The Quality and Relevance of the registry evaluated as appropriate
- 17 covariates clinically needed for balancing

1st Stage Design (2)

- Sample size: Trt 177, Con 177, power = 80%, significance level = 0.05
- Based on clinical/regulatory assessment (case-by-case basis), Enroll 177 (Trt) and 89 (Con) patients in the current investigational study, and Borrow 88 (Con, nominal) patients from the external registry

1st Stage Design (3)

- Propensity score method for reducing selection bias: **study** (trt+con) vs. **registry**(con)
- Covariates included in PS model: 17 covariates deemed as clinically important, collected in both the current study and the registry
- For PS modeling, subjects were selected first from the registry based the set of inclusion and exclusion criteria

1st Stage Design (4)

- PS stratification: 5 equal size strata for the current study, then the subjects from the registry are grouped into the strata according to its PS
- Covariates balance criteria: visual qualitative examination (density/bar plot)
- Iterative process until agreement reached among stakeholders
- Independent statistician identified from University B

1st Stage Design (5)

- General form (weighted product of density function):

$$L(\theta|Y) = \prod_{i=1}^{N} f(y_i|\theta)^{\lambda_i}$$

where λ_i is weight to be chosen.

- $\lambda_i = 1$, if the patient i is from the investigational study
- $0 < \lambda_i \leq 1$, if the patient i is from the external data source
  - Weight used to discount patient info from external data source
  - E.g. If $\lambda_i = 0.6$, 60% of this patient's info is borrowed and 40% discounted.

Ref.

- Lindsay, BG (1988). Composite likelihood method. *Contemporary mathematics*, 80(1): 221-239.
- Varin et al (2011). An overview of composite likelihood methods. *Statistics Sinica*, P5-42.

1st Stage Design (6)

SAP: Estimating the treatment effect

- The primary endpoint rates are estimated for treatment and control group in each stratum using the composite likelihood
- Take the difference in each stratum
- Average the difference across the strata
- Using jack-knife to get the variance

2nd Stage Design (1)

By the independent statistician

- Start as soon as enrollment of the current study is finished
- Propensity score modeling, forming PS strata, checking covariates balances

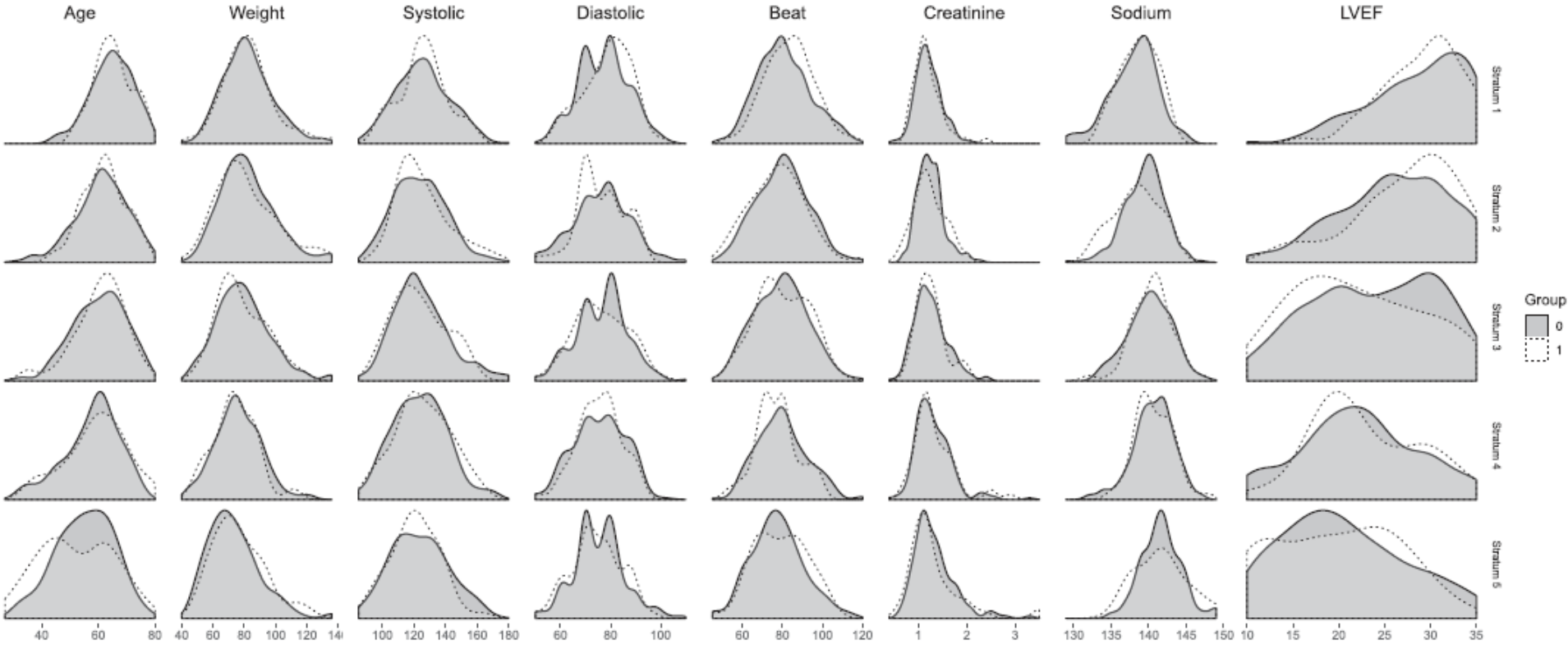
2nd Stage Design (2)

Number of subjects from current study and external registry within each PS stratum

		Propensity score stratum					
		1	2	3	4	5	Total
Current Study	TAVR	41	28	39	36	39	183
	Surgery	13	25	14	17	15	84
Registry	Surgery	332	270	233	201	156	1192

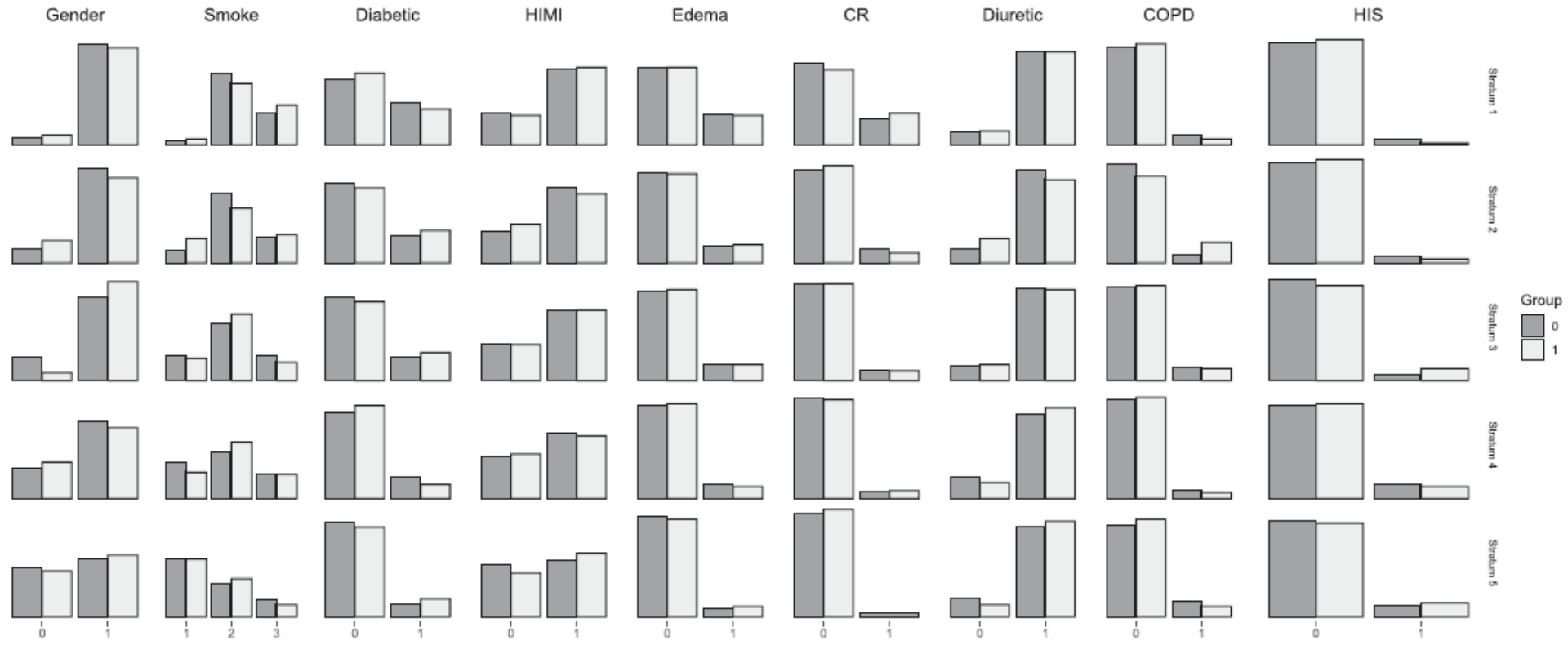
2nd Stage Design (3)

Density plots of covariates for current study and external registry by stratum



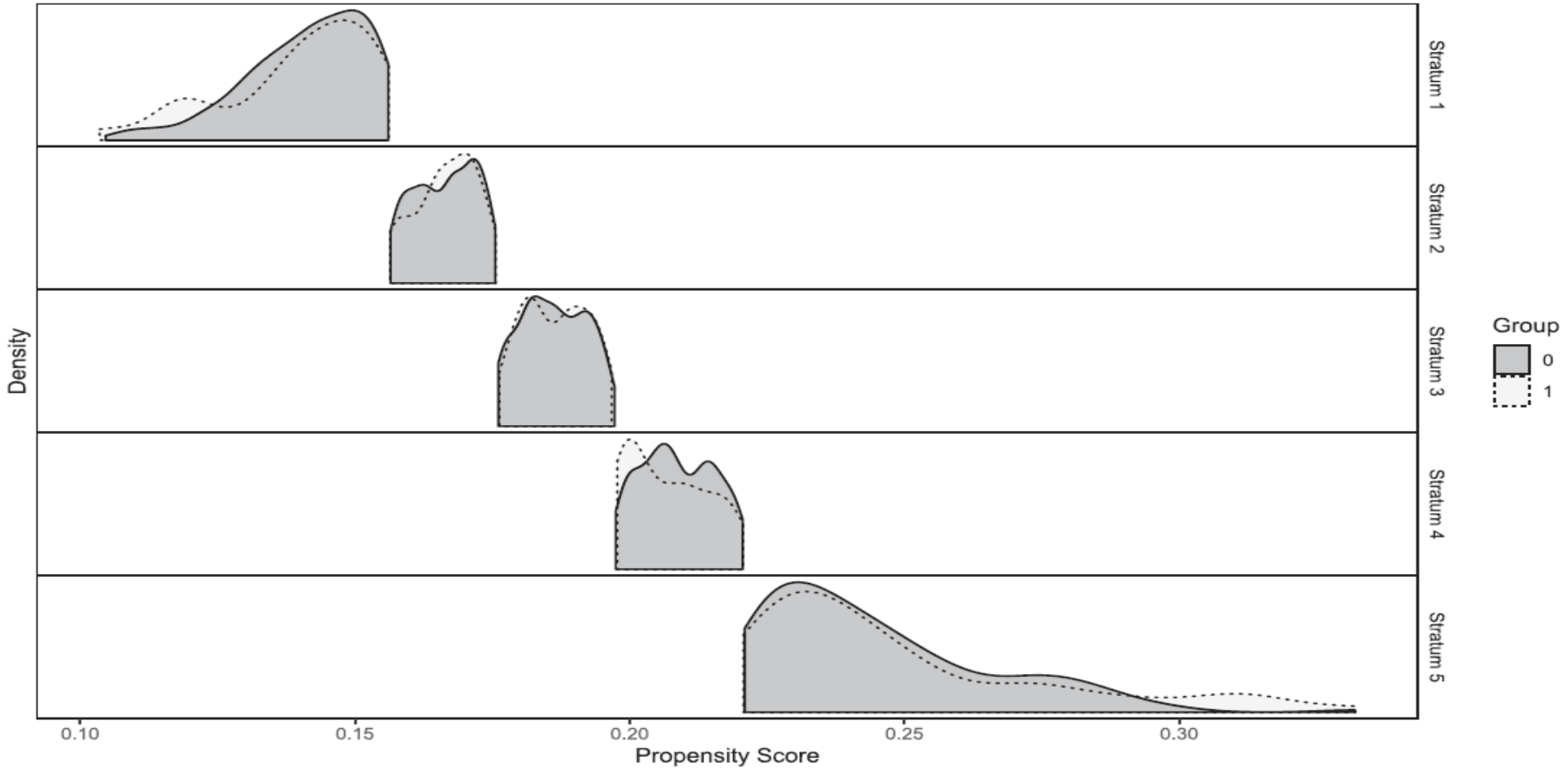
2nd Stage Design (4)

Bar plots of covariates for current study and external registry by stratum



2nd Stage Design (5)

Density plots of propensity scores for current study and external registry by stratum



2nd Stage Design (6)

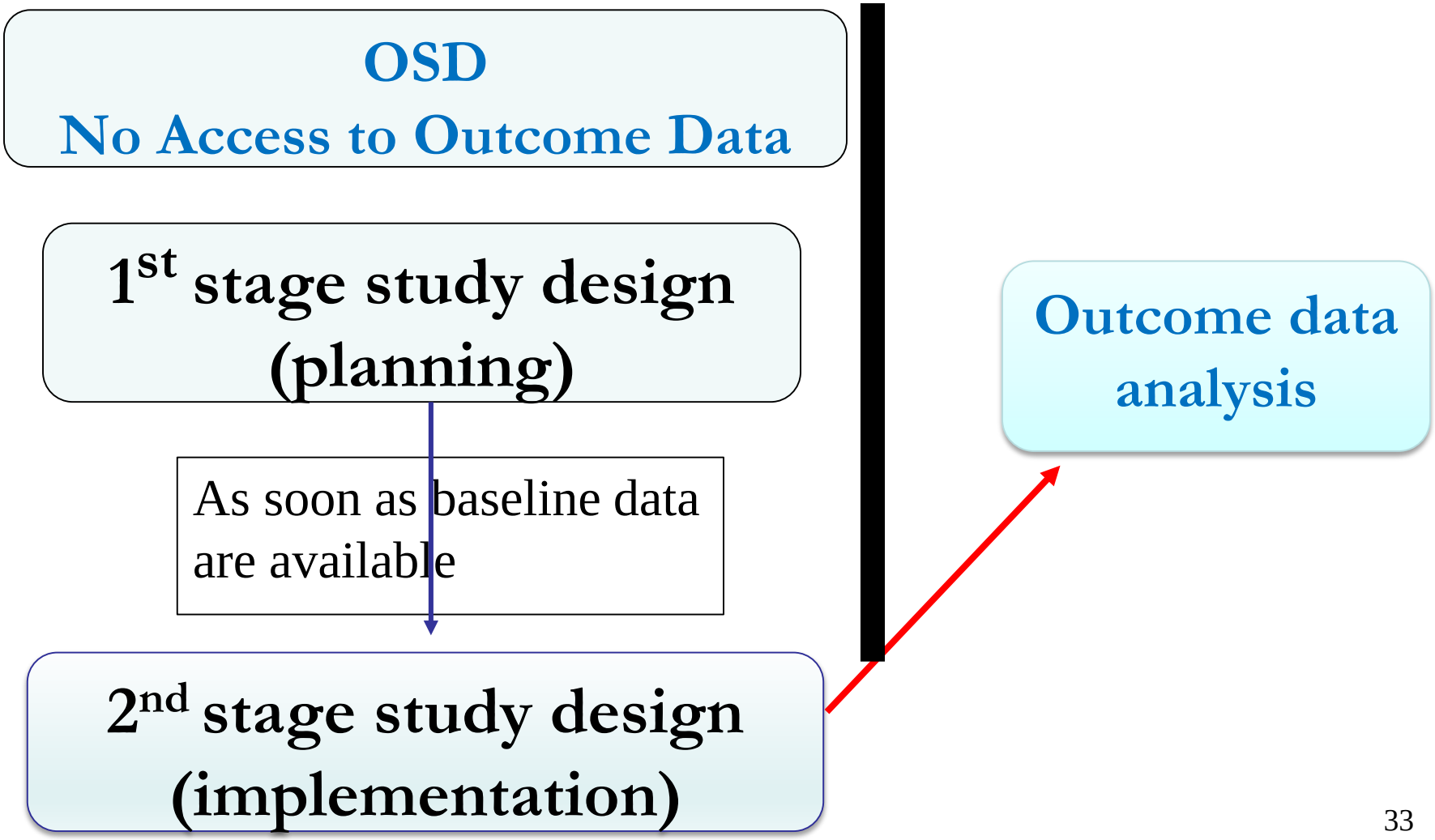
Full subject equivalents (Surgery) borrowed from external registry within each PS stratum

	Propensity score stratum					
	1	2	3	4	5	Total
Overlapping Coefficient	.85	.81	.82	.74	.82	
# of Subject	332	270	233	201	156	1192
# of Full Subject Equivalent (discount factor λ)	19 (.06)	17 (.08)	17 (.08)	16 (.08)	18 (.11)	87

2nd Stage Study Design (7)

- The independent statistician communicates the Design to the sponsor, and the Agency, and all agreed upon
- The 2nd stage design was finalized

Two-Stage Study Design Framework



Selected Work at CDRH

keep objectivity in regulatory decision making

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- Xu Y., Lu N., Yue L., Tiwari R. (2019). A study design for Augmenting the Control Group in a Randomized Controlled Trial; A Quality Process for Interaction Among Stakeholders. *TIRS* 1-6.

Thanks for your attention!