Objective Study Design for Using External Control in Pre-Market Evaluation of Medical Devices: A Discussion with Examples

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Outline

- Examples where external control is used
- Points to consider for selecting external control
- Objective study design (OSD)
- An illustrating example of OSD

External Control: Data Sources
in Pre-Market Evaluation of Medical Devices

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

Using External Control: A Long History

- P0980012/S004, panel meeting in 2004

  LVAD, two-arm nonrandomized study with a historical control

  https://wayback.archive-it.org/7993/20170404065525/https://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4051b1.htm

Using External Control: Recent Examples (1)

- P140031/S010, 3rd generation device (2nd generation device study as control, the same patient population) https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010B.pdf

Using External Control: Recent Examples (2)

- P100047, selected a contemporaneous control from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)
  https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047B.pdf

Using External Control: Limitations

- Selection bias
- Temporal bias
- Conduct bias
- Data quality (esp. for RWD)

Control Group Selection (1)

In the protocol, elaborate similarities in

- Measurement in primary endpoints
- Clinically important Covariates
- Major aspects of study conduct

Control Group Selection (2)

- If the control group data are collected early, in the protocol, discuss any impact of changing medical practice on the primary endpoint over time

Control Group Selection (3)

- If the control group data are from a registry, in the protocol, elaborate any difference in the way how the patients are followed in terms of the endpoints

Control Group Selection (4)

- Don't exclude any patient from the control group patients based on his/her clinical outcome information

e.g. excluding subject with 1) no event AND 2) follow-up less than 12 months

Objective Study Design (OSD) for using external control

- "Outcome-free" prospective study design is essential to ensure the scientific validity of analysis of clinical outcome data when external control is used
- Especially true as confirmatory evidence for regulatory decision-making

OSD: a Two-Stage Design

1st Stage

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

2nd Stage

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

An Illustrative Example of OSD

- Investigational device group: an LVAD
- Control group: INTERMACS registry (prospective)
- Primary endpoint: survival at 180 days, which is defined as alive on the originally implanted device or transplanted or explanted for recovery

1st Stage Study Design

In addition to the usual considerations such as patient population of interest, primary endpoint(s), and sample size planning, there are two unique considerations:

1) Quality of the registry data
2) Implementation plan for the reduction of selection bias

1st Stage: Quality of the Registry Data

- Primary endpoint: the same definition and adjudicated by an CEC
- Inclusion of patients: the same inclusion/exclusion criteria applied, in the same time period, and at the same clinical sites
- Data completeness and accuracy acceptable

1st Stage: Implementation Plan for the Reduction of Selection Bias (1)

- Specification of covariates: sex, lesl, lmld, rvd, lad, diab
- Statistical approach to balance those covariates: PS stratification (5)

1st Stage: Implementation Plan for the Reduction of Selection Bias (2)

- Assessment methods and criteria for covariate balance: boxplots and bar plots (visual), and standardized differences (0.25)
- Identification of an independent statistician to perform the 2nd stage design: a statistician from University B

2nd Stage Study Design (1)

- With access to the covariate data only, the independent statistician estimates the propensity scores and performs the study design to achieve balance in the specified covariates between the current study and external control groups

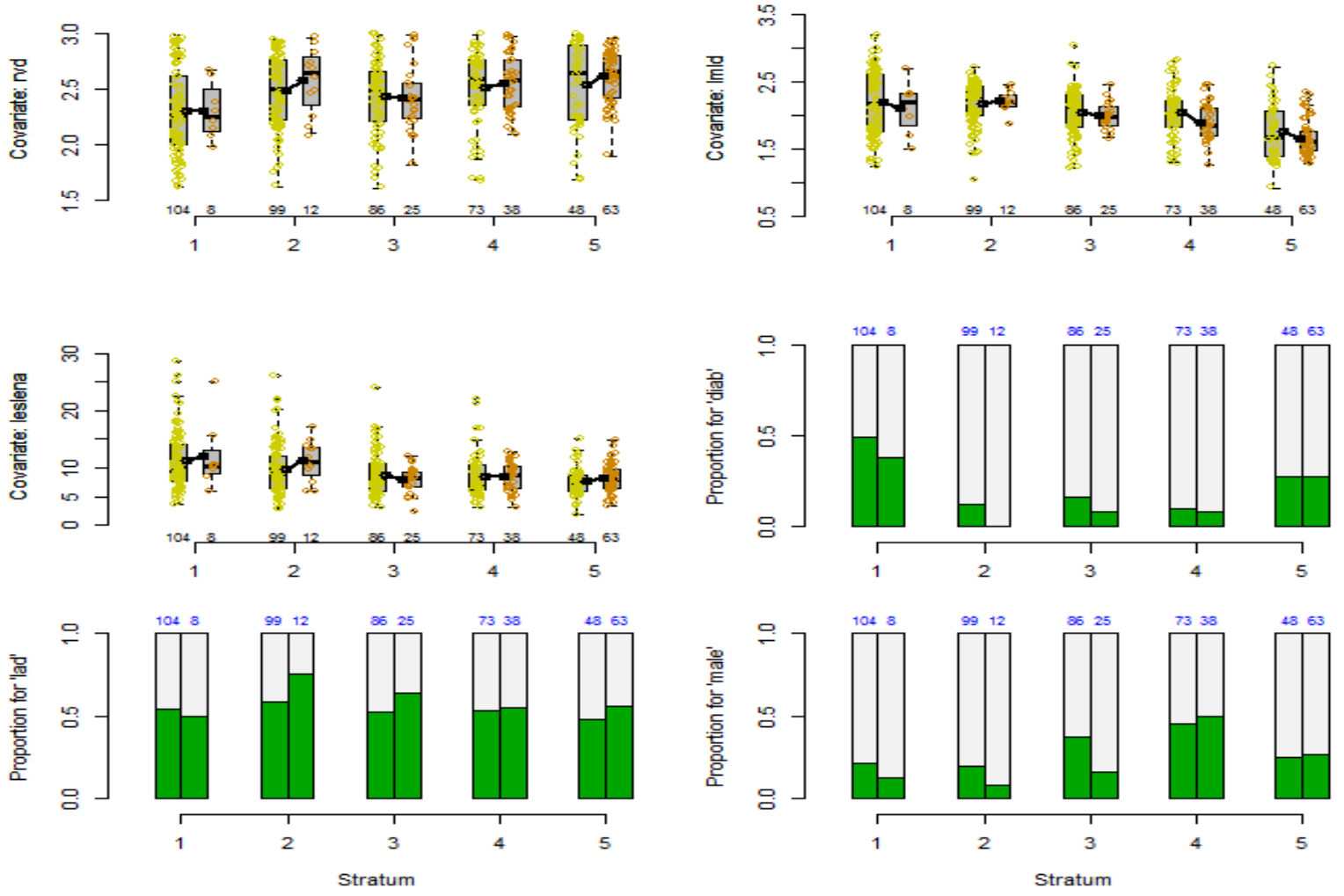
2nd Stage Study Design (2)

- Throughout the design process, the stakeholders communicate with each other to reach a consensus on whether the balance of the specified covariates is satisfactory for the resulting design.

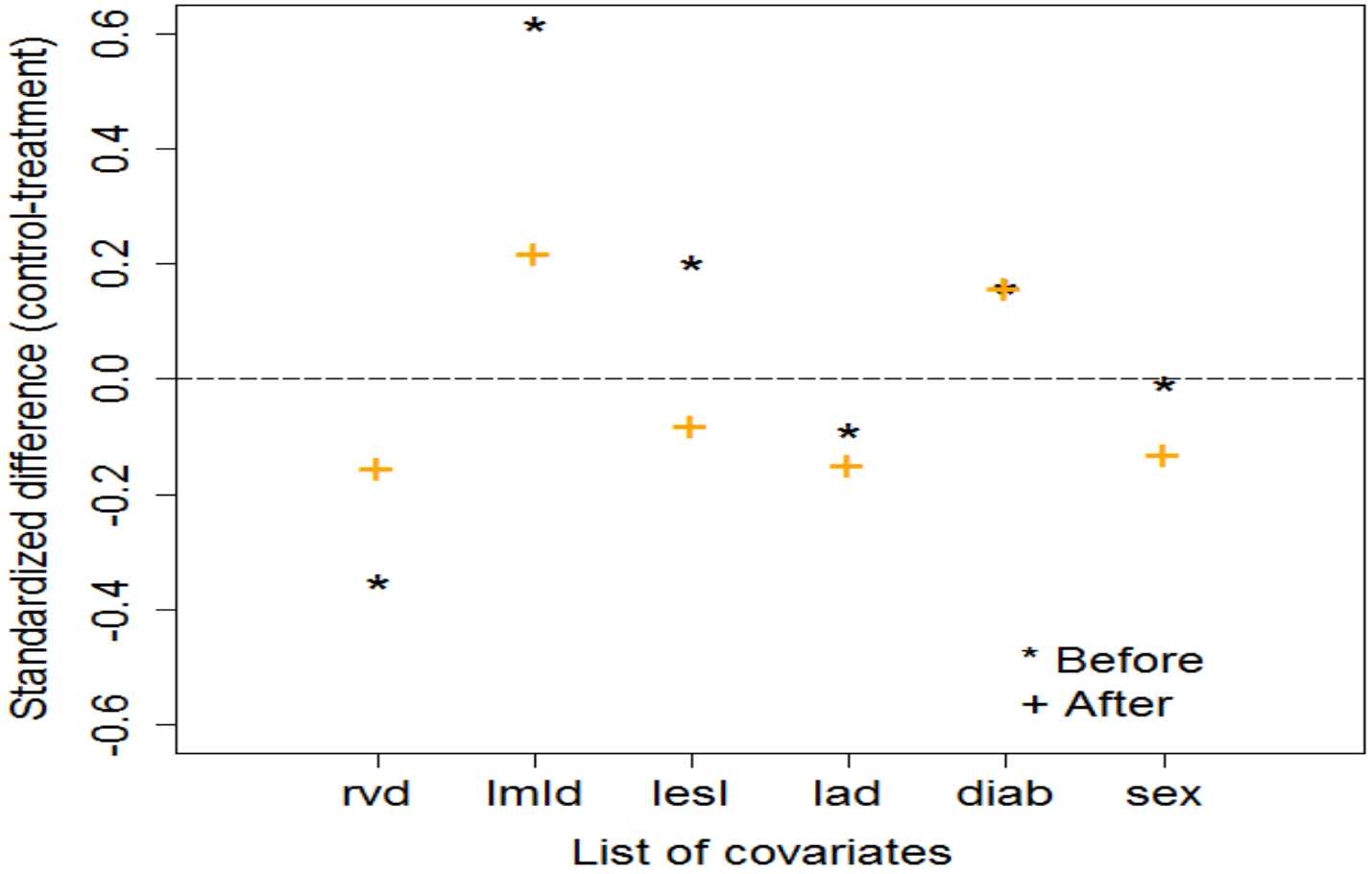
2nd Stage Study Design (3)

- The independent statistician communicates with all stakeholders, including FDA. Only when all stakeholders are satisfied with the results shown in Figures 1 & 2, and Table 1, move on to the next step (outcome analysis)

2nd Stage Study Design: Fig 1



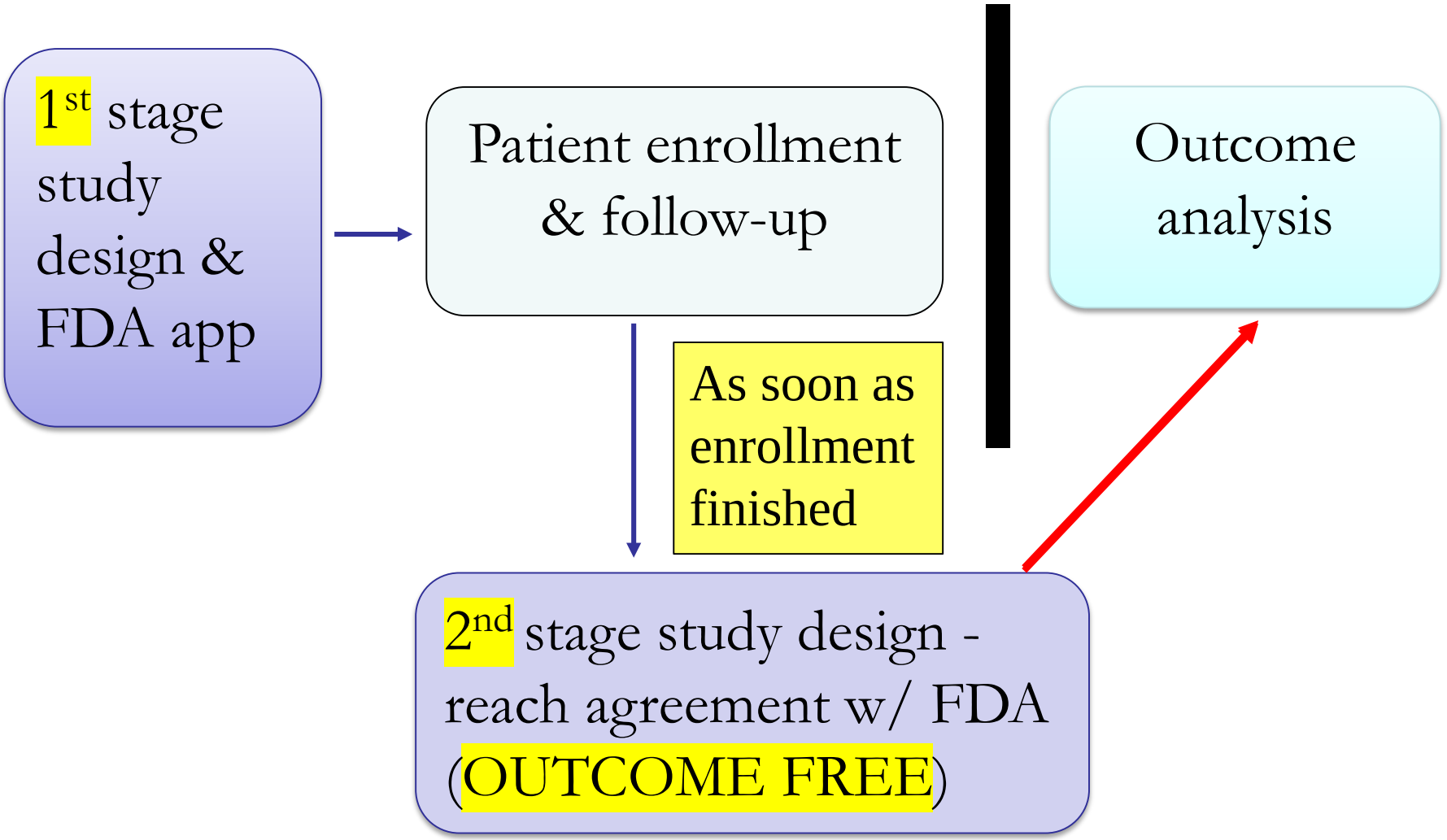
2nd Stage Study Design: Fig 2



2nd Stage Study Design: Table 1
Patient Distribution

Group	Propensity score stratum					
	1	2	3	4	5	Total
Trt	8	12	25	38	63	146
Con	104	99	86	73	48	410

Summary: A Two Stage Design Process for OSD



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Thanks for your attention!