Examining the Validity of External Controls Relative to Randomized Controls: The Essential Role of Data Quality

Introduction

Validity of External Controls in Medical Product Development

External controls are often considered less valid than randomized controls due to selection and confounding biases

To improve their validity

- High quality external data with accurate and considerable capture of prognostic variables and outcomes is needed to reduce selection bias
- Causal inference methods can reduce confounding

Can selection and confounding biases be sufficiently minimized so that external controls will replicate the results of a randomized control?

Three Case Studies in Oncology

Non Small Cell Lung Cancer (NSCLC) with docetaxel trt

Research Goal
Examine whether external control will replicate the estimation of overall survival from a randomized control

Data Source
Completed randomized controlled trials

Statistical Methods
Nearest neighbor 1:1 Propensity Score Matching

Case Study Status
Complete

RR Multiple Myeloma (RRMM) with dexamethasone trt

Research Goal
Examine whether external control will replicate the estimation of overall survival from a randomized control; explore methods to address unknown confounding

Data Source
Completed randomized controlled trials

Statistical Methods
Propensity Score Full Matching

Case Study Status
Complete

Pancreatic Cancer (PC) with gemcitabine and nab-paclitaxel trt

Research Goal
Examine whether external control will replicate the estimation of overall survival from a randomized control and whether this varies across data sources

Data Source
Multiple real word data sources and Completed randomized controlled trials

Statistical Methods
Propensity Score Matching and Weighting

Case Study Status
Ongoing

Case Study in Non Small Cell Lung Cancer

Identification of previous NSCLC trials

Identification of all applicable trials using publicly available resources, such as clnicaltrials.gov

Narrowed to trials with patient level data available through data sharing programs or other access

Trial selection was not designed to be impacted by study level outcomes and was completed without intentional knowledge of study level results

Data Sources

Project Data Sphere[1]

Medidata Enterprise Data Store (MEDS)[2]

Trial Characteristics

Open label and blinded phase 2 & 3 trials

Multinational

Timespan of starts of trials (2004 to 2013)

Overall survival measured[2]

1. These analyses are based on research using information obtained from Project Data Sphere, which is maintained by Project Data Sphere, LLC. Neither Project Data Sphere, LLC nor the owner(s) of any information from the web site have contributed to, approved or are in any way responsible for the contents of this work.
2. Includes thousands of previous clinical trials conducted by the pharmaceutical industry for drug or medical product development with patient level data recorded through the Medidata electronic data capture system. Legal agreements permit use in deidentified (i.e., patients and original sponsor of the trial cannot be identified) and aggregated (i.e., every analysis must include data from two or more sponsors) form. For more information visit the Medidata Data Collaboration Program.

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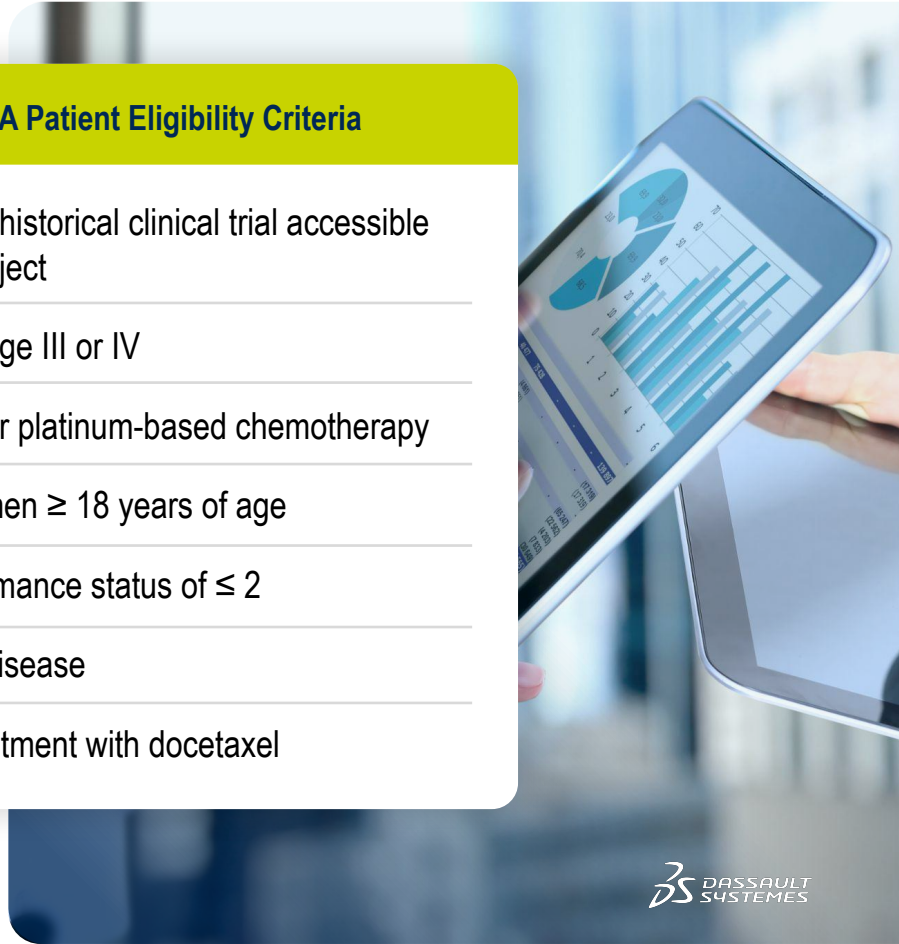
Data Preparation

- Standardization of variable definitions across trials
- Prespecified fully documented logic for variable derivation
- Availability of prognostic factors within reasonable time surrounding index date

SCA Patient Eligibility Criteria

- Inclusion in a historical clinical trial accessible within this project
- NSCLC at stage III or IV
- Received prior platinum-based chemotherapy
- Men and women ≥ 18 years of age
- ECOG performance status of ≤ 2
- Measurable disease
- Received treatment with docetaxel



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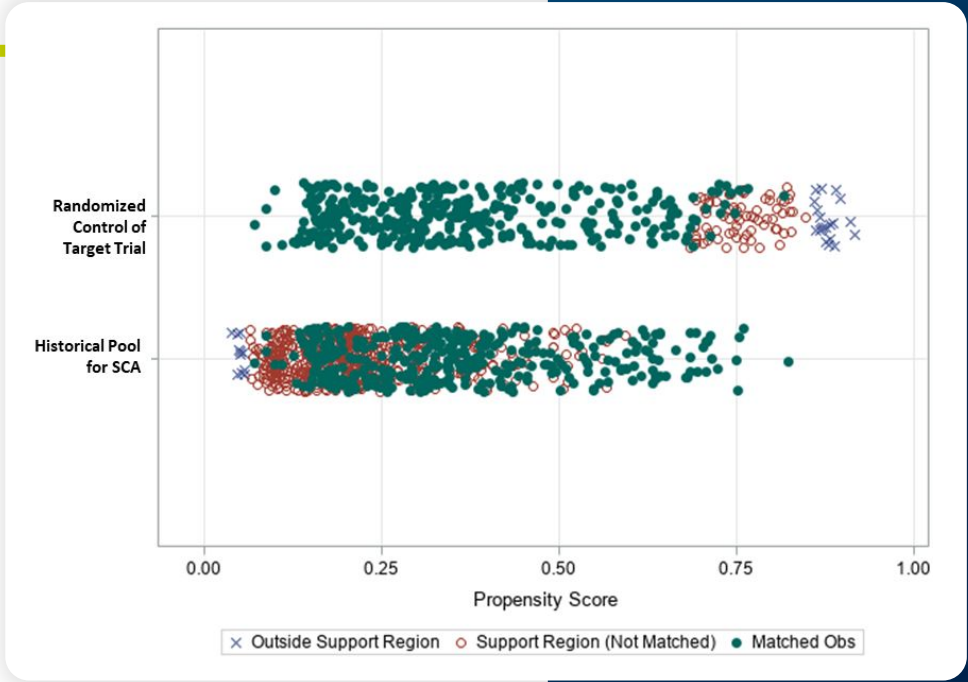
Prespecified Propensity Score Matching

- Age at baseline (continuous)
- Years from cancer diagnosis (continuous)
- Race (White vs Others)
- Sex (Female vs Male)
- Smoking (Current vs Former vs Never)
- Histology (Squamous vs Non-squamous)
- Stage (III vs IV)
- ECOG (0 vs 1 vs 2)
- Prior surgery (Yes/Maybe vs No)
- EGFR/KRAS mutation (Positive vs No/Unknown)



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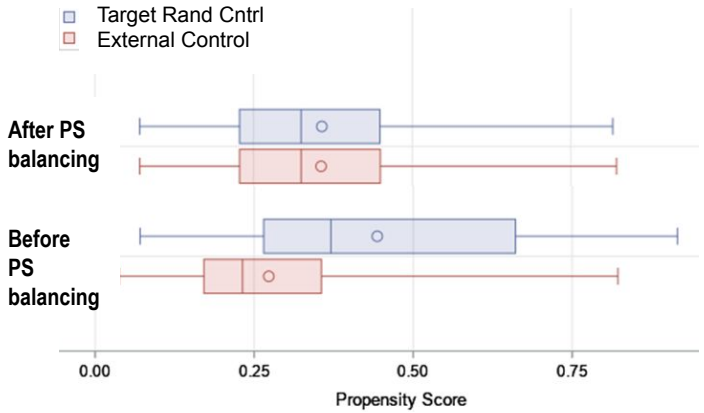
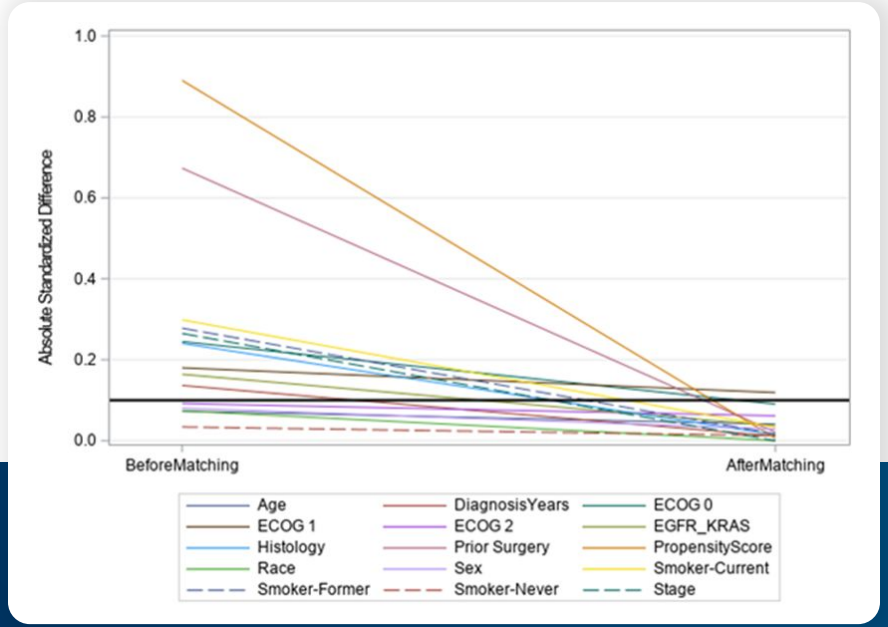
Baseline Comparability of External and Randomized Control

Considerable imbalance before matching; Similar propensity score distributions after matching





Overall Survival

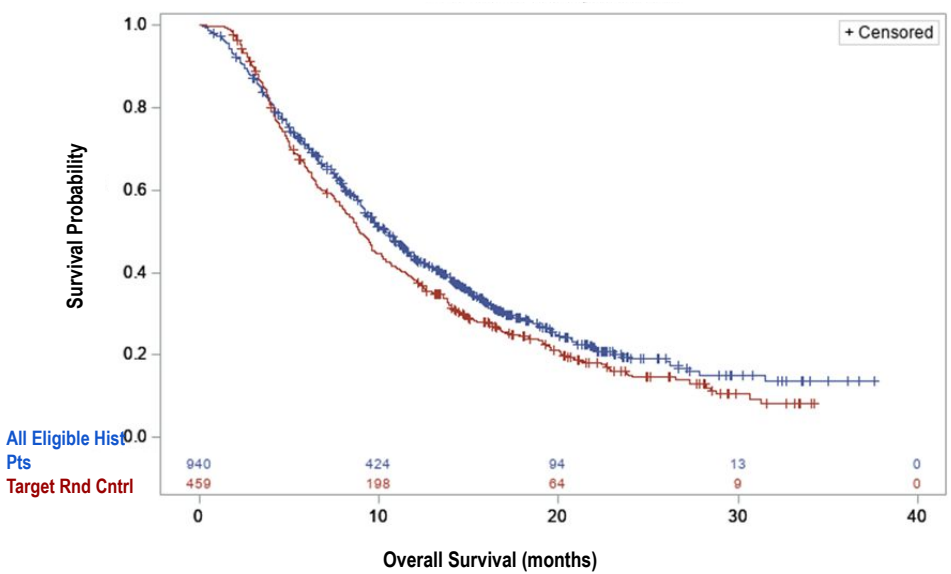
All Eligible Historical Patients vs. Randomized Control

Before PS Matching

Overall survival estimates are not aligned

Separation between curves

Stat sign log rank test (p=0.03) and hazard ratio (1.16 with 95% CI 1.02, 1.32)



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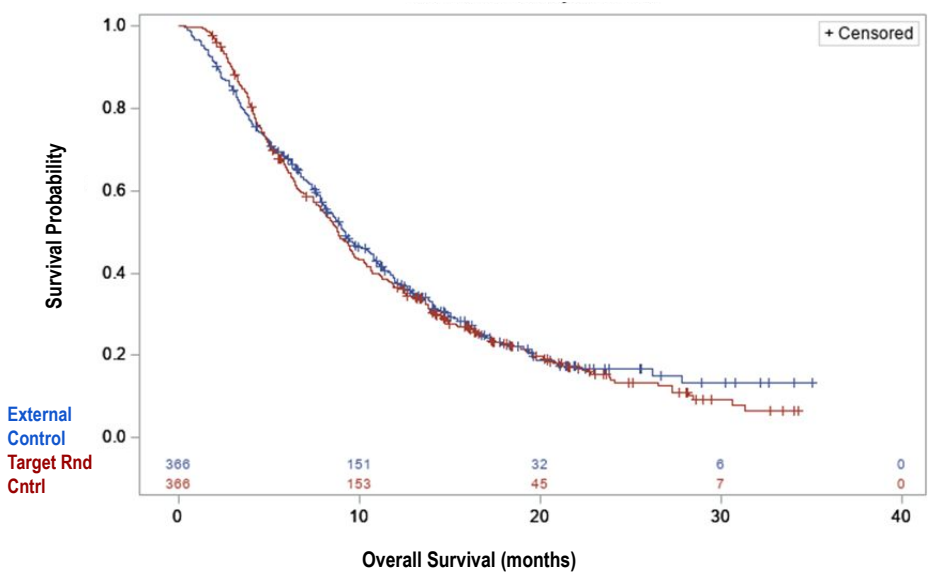
Overall Survival

PS Balanced External vs. Randomized Control

After PS Matching
Overall survival estimates are aligned

Little separation between curves

Stat insignificant sign log rank test (p=0.65) and hazard ratio (1.04 with 95% CI 0.88, 1.23)



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Case Study in Relapsed Refractory Multiple Myeloma

Identification of previous RRMM trials

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Trial selection was not designed to be impacted by study level outcomes and was completed without intentional knowledge of study level results

Data Sources

Medidata Enterprise Data Store (MEDS)[1]

Trial Characteristics

Open label phase 3 trials

Multinational

Timespan of trial conduct (2010 to 2017)

Overall survival measured

1. Includes thousands of previous clinical trials conducted by the pharmaceutical industry for drug or medical product development with patient level data recorded through the Medidata electronic data capture system. Legal agreements permit use in deidentified (i.e., patients and original sponsor of the trial cannot be identified) and aggregated (i.e., every analysis must include data from two or more sponsors) form. For more information visit the Medidata Data Collaboration Program.

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Data Preparation

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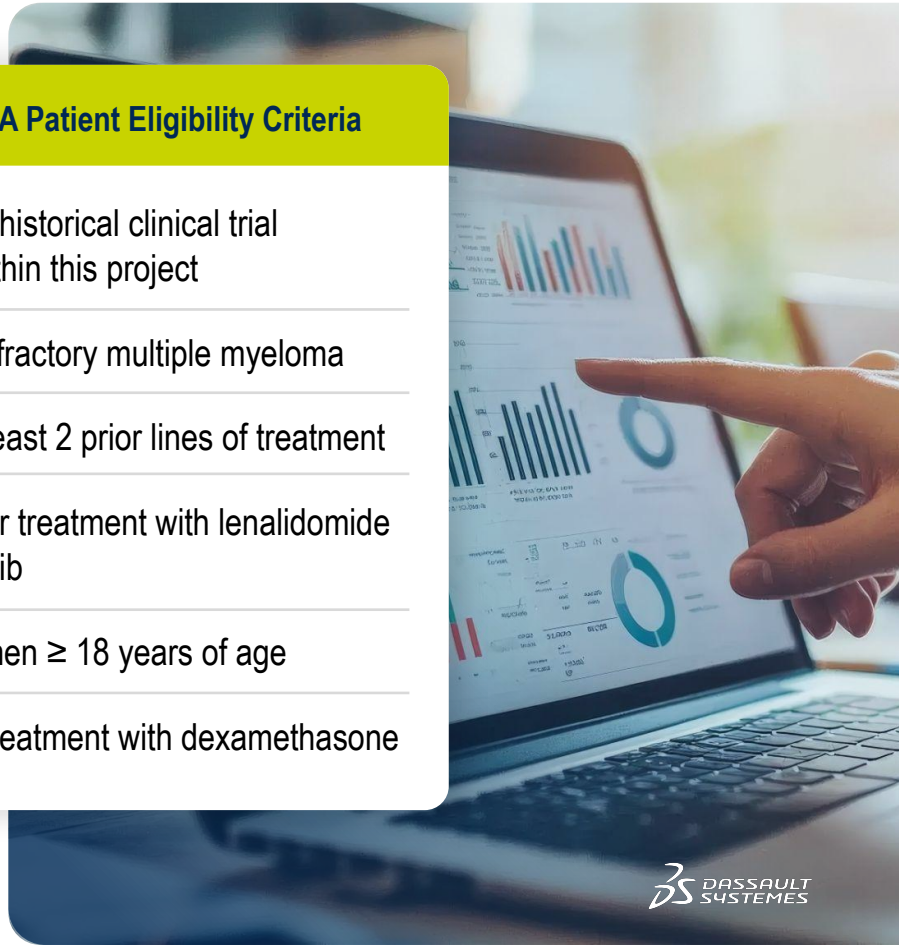
- Availability of prognostic factors within reasonable time surrounding index date

SCA Patient Eligibility Criteria

- Inclusion in a historical clinical trial accessible within this project
- Relapse or refractory multiple myeloma
- Received at least 2 prior lines of treatment
- Received prior treatment with lenalidomide and bortezomib
- Men and women ≥ 18 years of age
- Assigned to treatment with dexamethasone



Overall Survival

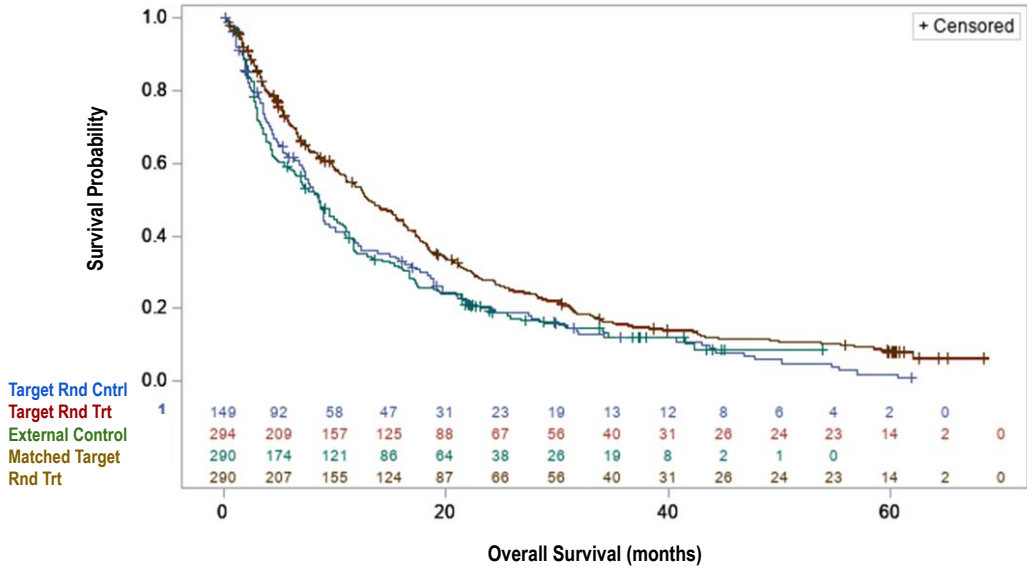
PS Balanced External vs. Randomized Control

After PS Matching
Overall survival estimates are aligned

Little separation between control curves

Consistent inference regarding Trt Effect

- With Randomized Cntrl
  HR 0.74 (0.60, 0.92); log rank p=0.006
- With External Cntrl
  HR 0.76 (0.63, 0.91); log rank p=0.016



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Case Study in Pancreatic Cancer

Validity of External Controls created from RWD or Historical Clinical Trials Data in Pancreatic Cancer

Phase 1
Project Scoping

- Identify and assess data partners for RWD and historical trial data.
- Select target RCTs and define key criteria for ECA feasibility.
- Align on patient characteristics, endpoints, and matching methods.
- Evaluate data gaps and implementation readiness.

Phase 2
Project Design

- Adapt RCT eligibility criteria to external datasets and standardize variable definitions.
- Define baseline characteristics & covariates for propensity modeling.
- Draft the Statistical Analysis Plan and align on standardized population reporting.
- Coordinate with the sponsor to obtain Target trial data.

Phase 3
Pilot Execution

- Define study population using I/E criteria.
- Finalize SAP based on feasibility.
- Data partners build ECA and conduct analysis per SAP.
- Synthesize results and prepare findings for dissemination in 2025/2026.

The ECA Pilot Project Workflow

Project Goal

Collaboratively define a robust process for ECA construction using patient-level RWD and prior clinical trial data to evaluate its applicability for replicating the population and efficacy results observed in target trial data

Use Case

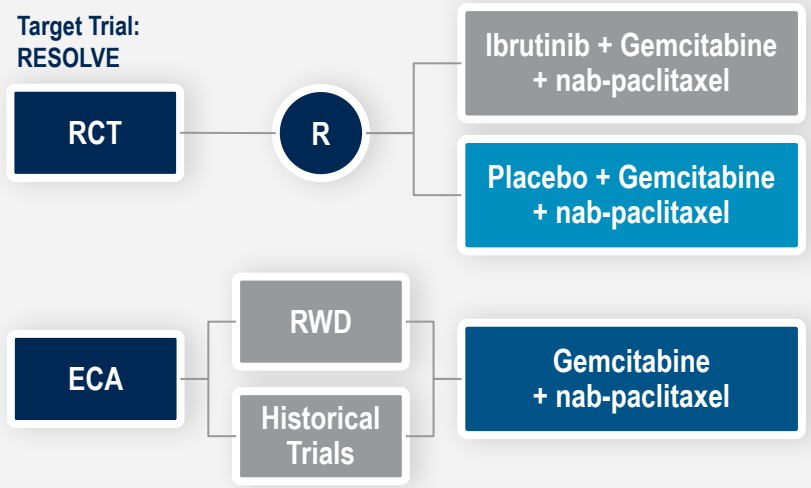
Metastatic pancreatic ductal adenocarcinoma (mPDAC)

- Relatively lower occurrence
- Unmet need (low survival rate)
- Standard of care relatively unchanged over time
- Completed RCTs to replicate
- Well-understood prognostic factors for propensity score matching/weighting

Regulatory Objectives

- **Establish criteria** for evaluating whether data are fit-for-purpose for use as an ECA
- **Identify characteristics** that make data sources similar to clinical trial data
- **Evaluate epidemiological and statistical study design and methods** for ECA

Approach to Constructing an ECA



- Applicable eligibility criteria will be selected based on the target trial.
- Propensity score methods will be applied to balance the baseline characteristics.

Conclusions

Selection and confounding bias can be reduced to an extent that an external control will mimic the results of a randomized control (even when the possibility of some unknown confounding still exists)

Data selection and quality are key

Propensity score methods substantially reduce confounding even after strict eligibility criteria were applied

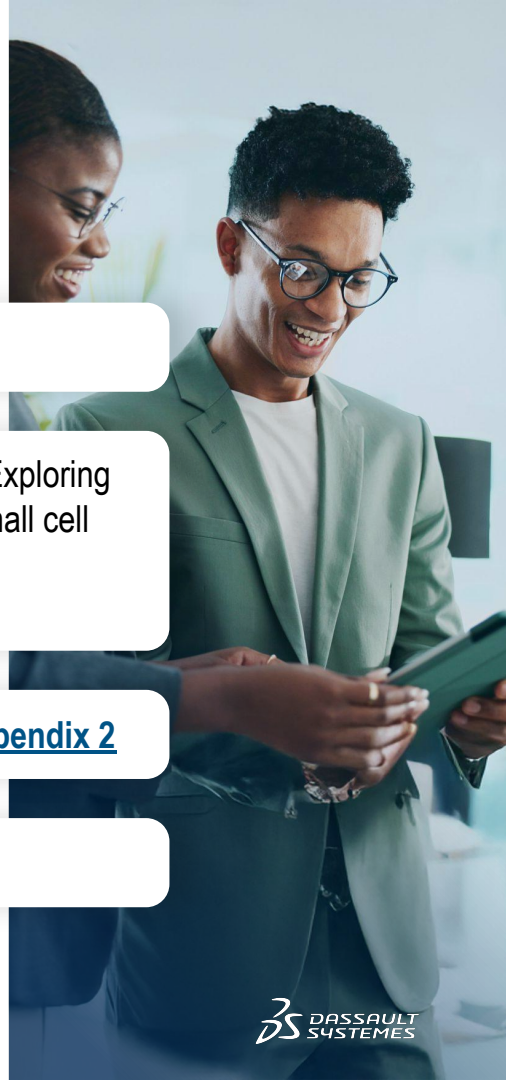
More information about the Friends of Cancer Research Case Studies

External Controls Case Study in Non Small Cell Lung Cancer White Paper

Yin, X., Mishra-Kalyan, P. S., Sridhara, R., Stewart, M. D., Stuart, E. A., & Davi, R. C. (2022). Exploring the Potential of External Control Arms created from Patient Level Data: A case study in non-small cell lung cancer. Journal of Biopharmaceutical Statistics, 32(1), 204–218. https://doi.org/10.1080/10543406.2021.2011901

External Controls Case Study in Relapsed Refractory Multiple Myeloma White Paper Appendix 2

External Controls Case Study in Pancreatic Cancer (ongoing)



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