Constructing a Synthetic Control Arm from Previous Clinical Trials, with Application to Cancer Trials

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Introduction to Synthetic Control Arms (SCAs)

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Clinical trials are hampered by absence of control group

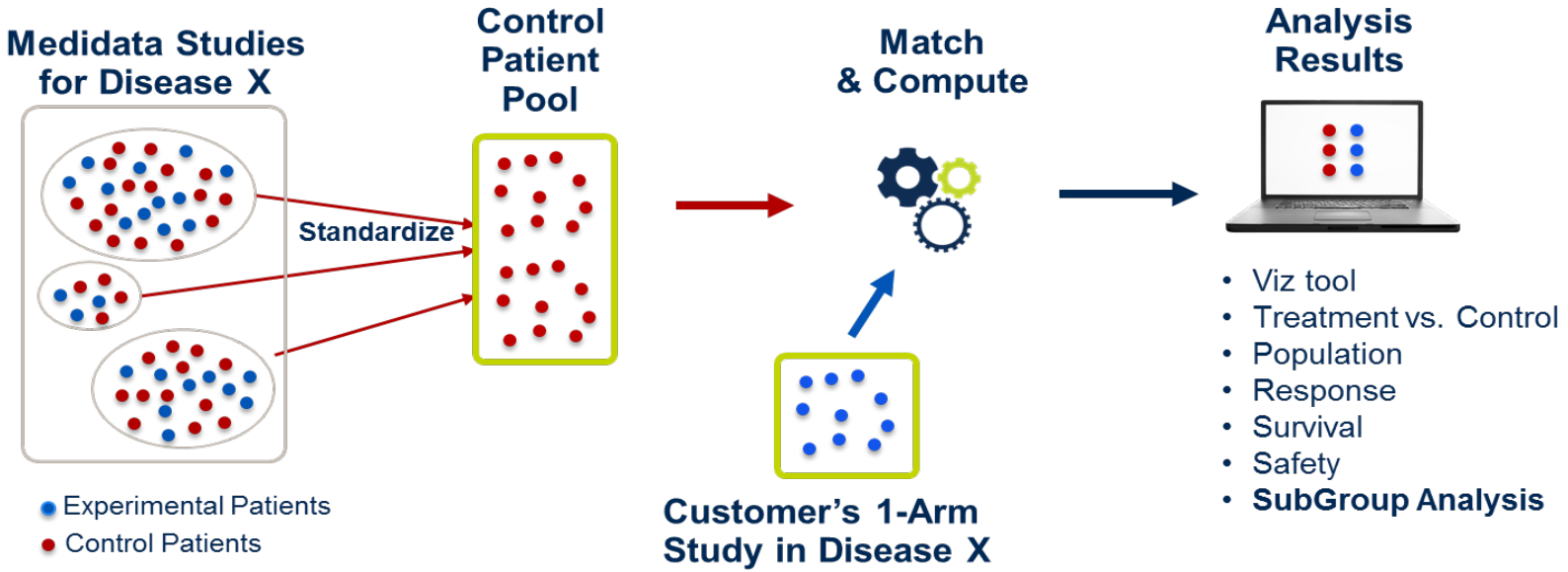
- Single-arm efficacy trials are often necessary, especially in early phase trials, because of
  - (a) Ethical concerns: when no effective treatment exists for serious & aggressive indications
  - (b) Practical concerns: when (i) patients resist allocation to control group ← (a); (ii) recruiting & retaining are hard → few patients are in trial → we need to allocate all of them to treatment group
  - (c) Difficult oncology indications → (a) & (b)(i)
  - (d) Rare diseases or populations (e.g., pediatrics) → (b)(ii)

Introduction to Synthetic Control Arms (SCAs)

- Expensive go/no-go decisions are often made on scant evidence
  - Historical control arm (HCA) approach is common: Compare experimental treatment results with published papers & abstracts
  - HCAs are controversial because:
    - Comparison is at *study level* rather than *patient level*
    - There is unknown statistical bias from patient baseline characteristics
    - Each historical trial has unique features
    - Trials differ in time and location
    - There are few metrics for similarities / differences among trials
    - Publication bias is present because unpublished trials are unavailable
  - Decisions sometimes based on subjective / anecdotal knowledge
- Limited evidence increases later-phase failure rate

Introduction to Synthetic Control Arms (SCAs)

SCA leverages prior control patient data to improve evaluation of outcomes of single-arm trials



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Introduction to Synthetic Control Arms (SCAs)

SCA has benefits across the development cycle

- Reduced scientific uncertainty in evaluating efficacy in early-phase trials
  - Arms are precisely matched at patient level
  - Control group can be large compared to treatment group
  - Bias from time, site, and study-specific effects is minimized
  - Exploratory subgroup analysis is enabled
- Improved selection of compounds for go-to-next-phase
- Improved design of subsequent trials
- Reduced failure rates in phases II and III

Relapse/Refractory (RR) AML Trial Overview

Roche single-arm trial of Treatment for RR AML

- 16 response-evaluable RR AML (Acute Myeloid Leukemia) patients enrolled and received treatment
- Prespecified primary efficacy endpoint (outcome variable) was confirmed CR/Cri (**C**onfirmed **R**esponse / **C**onfirmed **R**esponse with **i**ncomplete blood count recovery)
- Inclusion criteria:
  - ≤ 2 prior regimens
  - Age ≥ 18
  - ECOG score = 0 or 1: normal activity is possible

Relapse/Refractory (RR) AML Trial Overview

Trial objectives

- To assess feasibility of constructing an appropriate control arm data set, a Synthetic Control Arm (SCA), by aggregating patient-level data from historical clinical trials.
- To reduce biases common to studies with historical control arms by using the SCA in estimation of the treatment effect.
- To evaluate response association with survival as an exploratory analysis.

Methodology for the SCA

- **Construct SCAs using patient-level data selected from standardized data repository of > 3,000 historical trials**
- **Oncology data available for SCA (May 2017):**

Indication	Subjects
Lung Cancer	27,252
Breast Cancer	19,520
Prostate Cancer	12,660
Colorectal Cancer	11,965
Multiple Myeloma	9,301
Kidney Cancer	7,388
Lymphoma	6,854
Other Oncology Indications	102,374
Total	197,314

Methodology for the SCA

Other Oncology Indications include:

Leukemia, Liver Cancer, Melanoma, Brain Cancer, Gastric Cancer, Neutropenia, Myelodysplastic Syndrome, Ovarian Cancer, Oral Cancer, Pancreatic Cancer, Sarcoma, Esophageal Cancer, Mesothelioma, Mucositis, Head and Neck Cancer, Bladder Cancer, Squamous Cell Carcinoma, Biliary Tract Cancer, Endometrial Cancer, Thyroid Cancer, Bone Metastases, Neuroblastoma, Multiple Conditions, and Other.

Methodology for the SCA

340 patients from 7 historical AML trials were available

- 10 SCA patients were selected (while blinded to outcome) to match each of the 16 treated patients on ≥ 4 of 6 baseline criteria at the individual patient level:

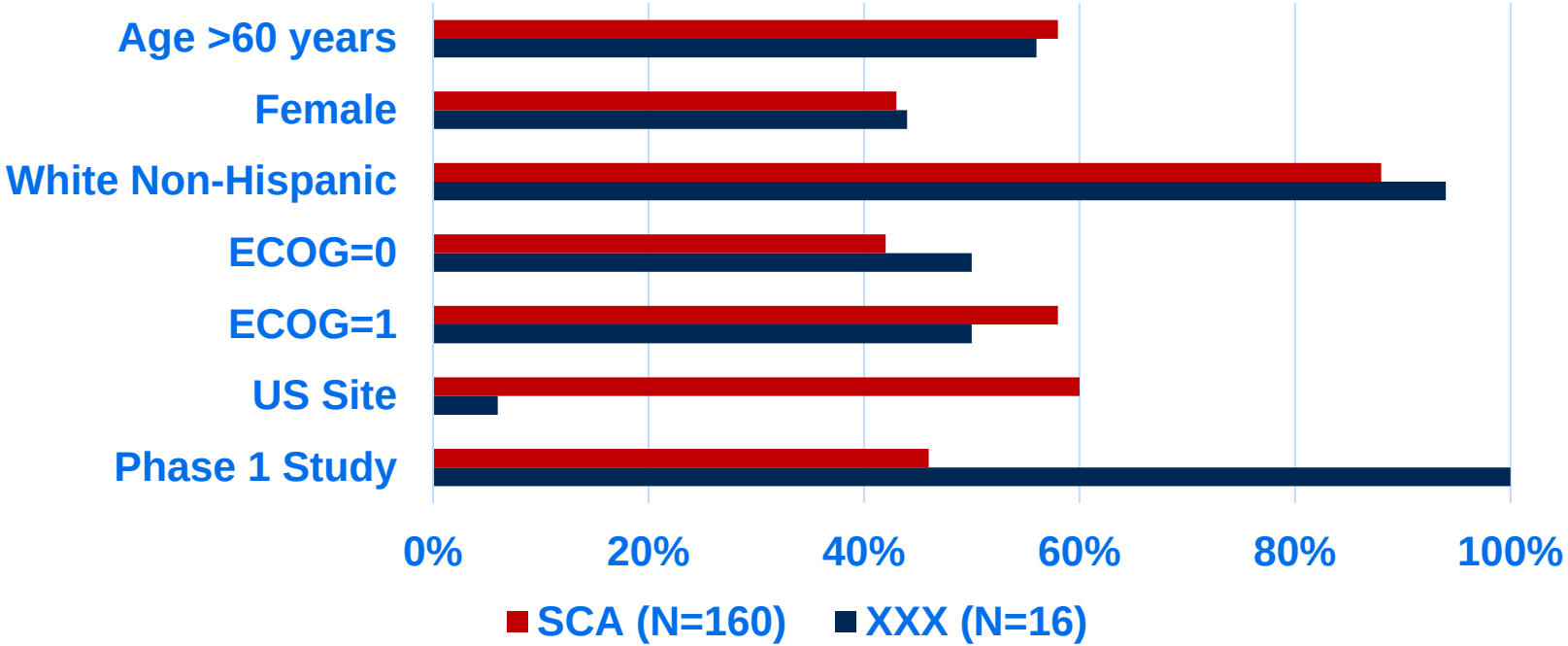
Age above or below 60 years	ECOG score
Sex	US site or not
White non-Hispanic or not	Phase of study

- Historical trial patients from both standard of care & experimental arms were used to increase sample size

  Reason: Historical experimental therapies had no apparent effect

Results for RR AML Study

Baseline Demographic & Disease Characteristics



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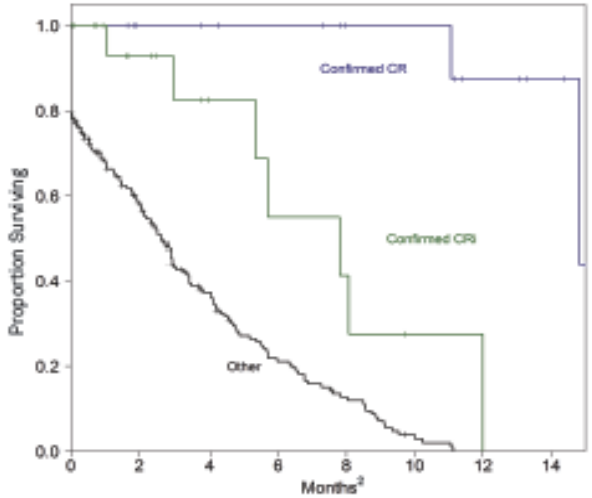
Results for RR AML Study

Patients who achieved confirmed CR had better overall survival than those who achieved confirmed CRi[1]



	N	Events	Median
Confirmed CR	16	2	14.8
Confirmed CRi	23	7	7.8
Other	254	172	2.6
Total	293	181	

	Hazard Ratio (95% CI)
Confirmed CR vs. Confirmed CRi	0.03 (0.001, 0.75)
Confirmed CR vs. Other	0.02 (0.002, 0.14)
Confirmed CRi vs. Other	0.24 (0.10, 0.54)

Synthetic Control Arms: Conclusions

SCAs provide enhanced context for interpretation of uncontrolled experimental results, enabling

- Quantitative estimation of treatment effect size
- More reliable decision making in early phases
- Exploratory analyses exploiting large sample size available from SCA supplementing small single-arm trial
- Construction of more efficient & informative clinical trials