Using Synthetic Control Databases to Accelerate Indication-Specific Safety & Efficacy Evidence

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1: INTRODUCTION

Synthetic control databases (SCD™) of recent clinical trial data are one potential tool for accelerating development programs.

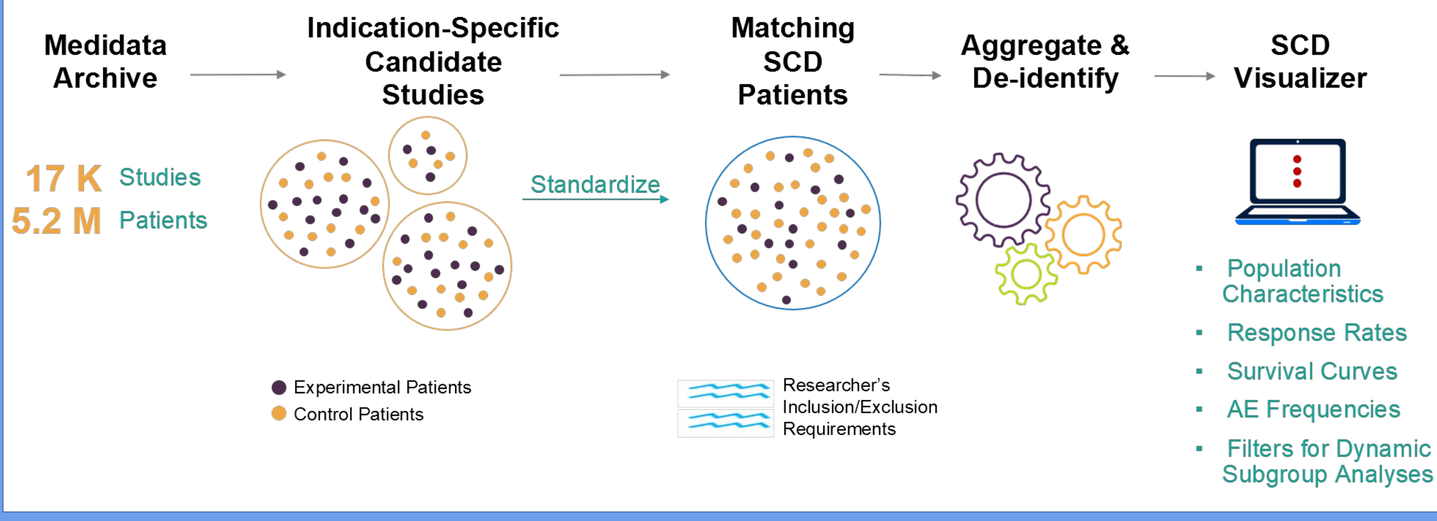
SCDs may provide rigorous pooled clinical data beyond that available in published literature and have certain strengths over real-world data (RWD).

SCDs may aid in understanding patient populations, target response rates, background AE rates including rare events, and relationship between variables.

A pilot has been ongoing to develop an SCD for metastatic breast cancer (mBC).

2: SCD CONCEPT

An aggregated dataset of hundreds (or thousands) of patients from multiple recent trials chosen to match a researcher's inclusion/exclusion criteria for an indication



3: SCD PILOT in mBC

Inclusion criteria:

mBC subtypes:

- Hormone Receptor positive, HER2 negative (HR+/HER2-) *OR*
- Triple Negative (TNBC)

Lines of therapy:

- 2nd or later line *OR*
- high-risk 1st line

Completed Phase II & Phase III open-label trials with RECIST endpoints

Medidata Rave® studies with data aggregation rights

Version 1 delivered Oct 2018 and updated quarterly

4: CURRENT STATUS

SCD as of May 2019 includes 1528 patients from 5-10 Phase II & III clinical trials

- 779 (51%) HR+/HER2-
- 749 (49%) TNBC

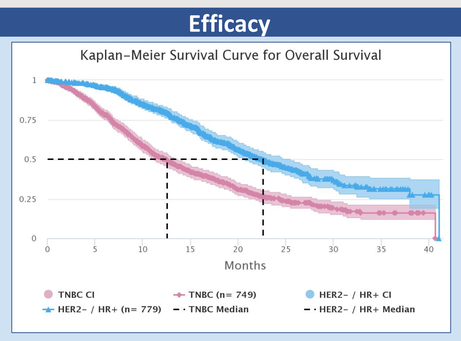
Large majority (>90%) of patients from trials in 2nd or later line of therapy

Includes >190 patient characteristic, efficacy and safety outcome variables

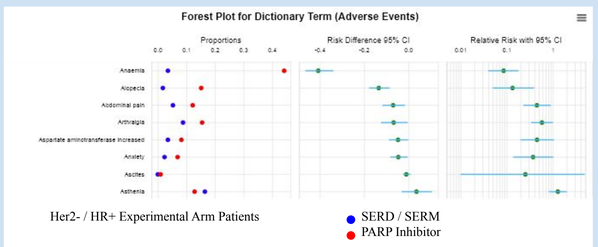
User accesses SCD by generating tabular and graphical summaries in interactive Visualizer. To protect re-identification, filtered subgroups are subject to 5/2 rule (at least 5 patients and 2 Sponsors)

5: EXAMPLE EXPLORATORY SUMMARIES USING THE SCD VISUALIZER

Efficacy

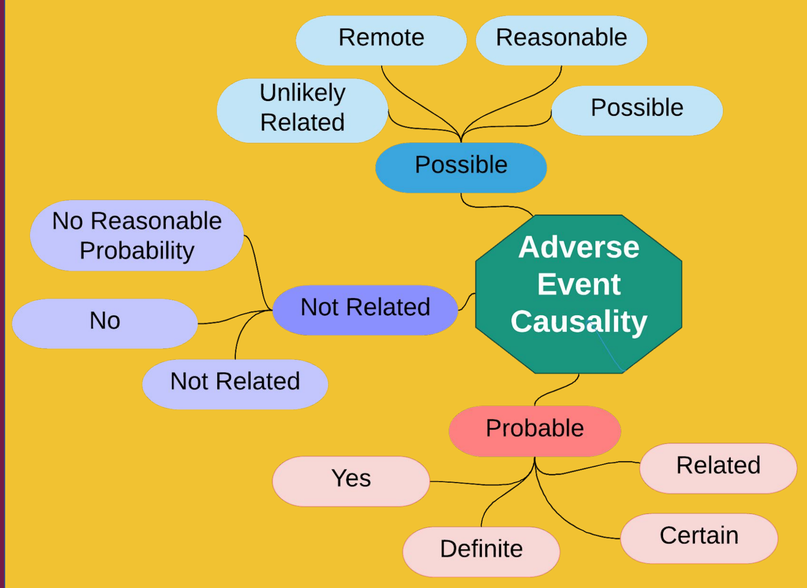


Safety



6: CHALLENGES

Terminology Standardization



Simpson's Paradox - Unadjusted comparisons can lead to misleading results

Ph 2 trial, 1:1 randomization Overall AE rate 1%

	Group 1	Group 2	
AE	1 (1%)	1 (1%)	2
No AE	99	99	198
	100	100	200

No increased risk of AE between Groups

Ph 3 trial, 2:1 randomization Overall AE rate 25%

	Group 1	Group 2	
AE	40 (25%)	20 (25%)	60
No AE	120	60	180
	160	80	240

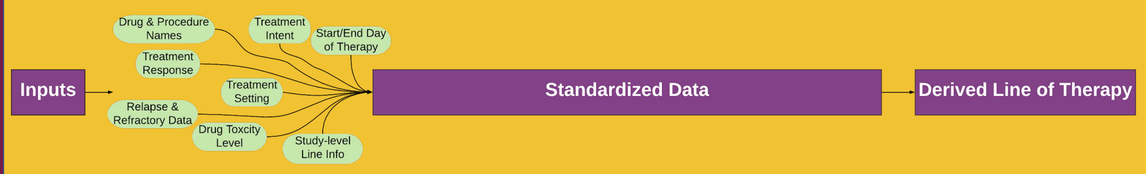
No increased risk of AE between Groups

Simple Pooling of both trials

	Group 1	Group 2	
AE	41 (16%)	21 (12%)	62
No AE	219	159	378
	260	180	440

Simpson's Paradox: Appears as if there is a higher AE rate (16% - 12% = 4%) in Group 1

Derivation of Complex Data Not Collected



Reported Term	Standardized Data					
	Preferred Term	Treatment Intent	Best Overall Response	Therapy Study Start Day	Therapy Study End Day	Drug Class
PACLITAXEL	paclitaxel	Curative		-2352	-2268	Taxanes
GOSERELIN	goserelin	Curative	CR	-2170	-1450	Endocrine therapy not otherwise specifed
TAMOXIFEN	tamoxifen	Curative		-2170	-1294	SERM
CYCLOPHOSPHAMIDE	cyclophosphamide	Adjuvant		-1268	-1207	Chemotherapy not otherwise specified
DOCETAXEL	docetaxel	Adjuvant		-1268	-1207	Taxanes
LETROZOLE	letrozole		SD	-1099	-456	AI
DENOSUMAB	denosumab			-988		Supportive Care
EXEMETHSANE	exemestane		PD	-456	-343	AI
EVEROLIMUS	everolimus		PD	-442	-343	Protein Kinase Inhibitors (mTOR inhibitor)
FULVESTRANT	fulvestrant		SD	-343	-175	SERD
NANOPARTICLE ALBUMIN-BOUND PACLITAXEL (ABRAXANE)	paclitaxel		PD	-133	-63	Taxanes

Curative & Adjuvant → Early Breast Cancer Therapy
1st Line
Filter Out Supportive Care
Start/End within 60 Days & Progressive Disease → 2nd Line
3rd Line
More toxic than previous therapy → 4th Line

Other Challenges

- Aggregating data to protect patient identification
- Different response assessment schedules
- Limited to clinical data captured in database - excludes data maintained externally (e.g., molecular)
- Possible publication bias regarding companies allowing data to be shared
- Blinded studies - cannot link patient characteristics/outcomes to treatment
- Small sample size in subpopulations

7: CURRENT USES OF PILOT SCD

Currently focus is on ***exploratory*** *questions via:*

- Dynamic filtering of SCD to aid understanding contemporary breast cancer populations. E.g., HR+/HER2- mBC contains heterogeneous subpopulations defined by treatment history (chemo eligible, CDK4/6i treated, etc.) and other characteristics.
- Benchmarking efficacy and safety outcomes for interpreting Ph 1b (often single-arm) studies and designing pivotal studies. HR+/HER2- mBC in particular has seen many recent shifts in SoC increasing this need.

8: CONCLUSIONS / FUTURE VISION

SCDs have potential to aid research programs and future study designs by providing data-driven benchmarks of clinical response, outcomes and safety, insights into disease subsets and correlations between short and long-term endpoints.

Arguably SCDs provide higher level data quality and patients who are more similar to clinical trial participants than real world data (RWD). However, questions addressed by SCDs are limited to the data collected in the underlying studies. Due to heterogeneity across studies in the type/format of data collected, substantial manual mapping and standardisation are required when creating the SCD. Industry standardisation (eg CRFs, data structure) will facilitate creation and use of SCDs.

If above challenges are addressed, possible future is for synthetic data to be incorporated in ***regulatory decisions***:

- External control arms in uncontrolled trials or supplementary controls in partially randomised trials
- Contemporary benchmarks (in combination with other sources of evidence) for interpreting safety signals and quantifying benefit/risk in support of regulatory submissions

9: DISCUSSION QUESTIONS

- Bias in excluding blinded trials from SCD?
- Synthetic control database vs Synthetic control arms?
- Vision for use in submissions or other use cases?
- Standardisation benefits?
- Combining with RWD?

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