

A Road Map to Standardize Historical Clinical Trials for Synthetic Control Arms®

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Introductions



Bhargav Koduru

Manager, Statistical Programming, Clinical Data Standards

- Former Statistical Programmer at SEAGEN, Sarepta, and Bioclinica.
- Expertise in Clinical Data Standards Implementation.
- MS Quantitative and Systems Biology, UCM
- MSc (Medical) Biochemistry, Manipal University



Corinne Ahlberg

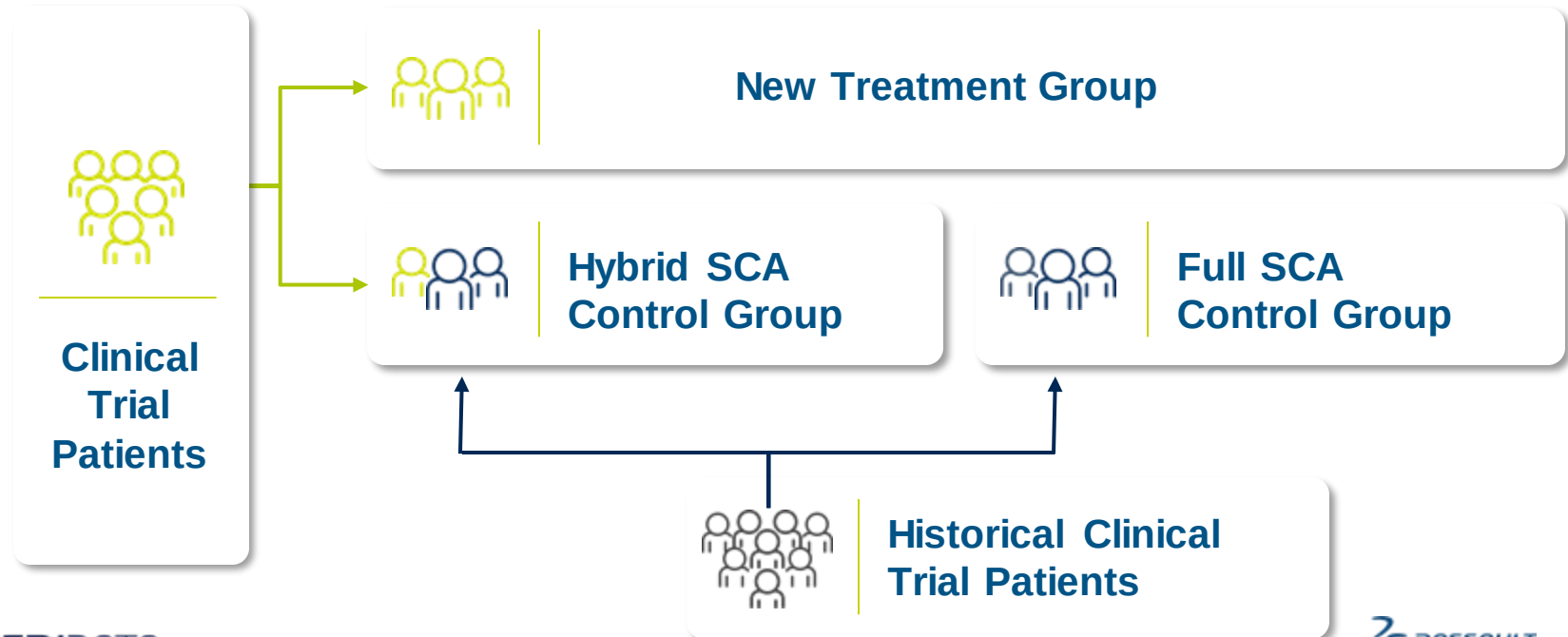
Director, Statistical Programming, Statistical Applications

- Former statistical programmer at Children's Hospital of Philadelphia, PPD and PRA
- Expertise in statistical programming and clinical data standardization
- MS Applied Statistics, Villanova University

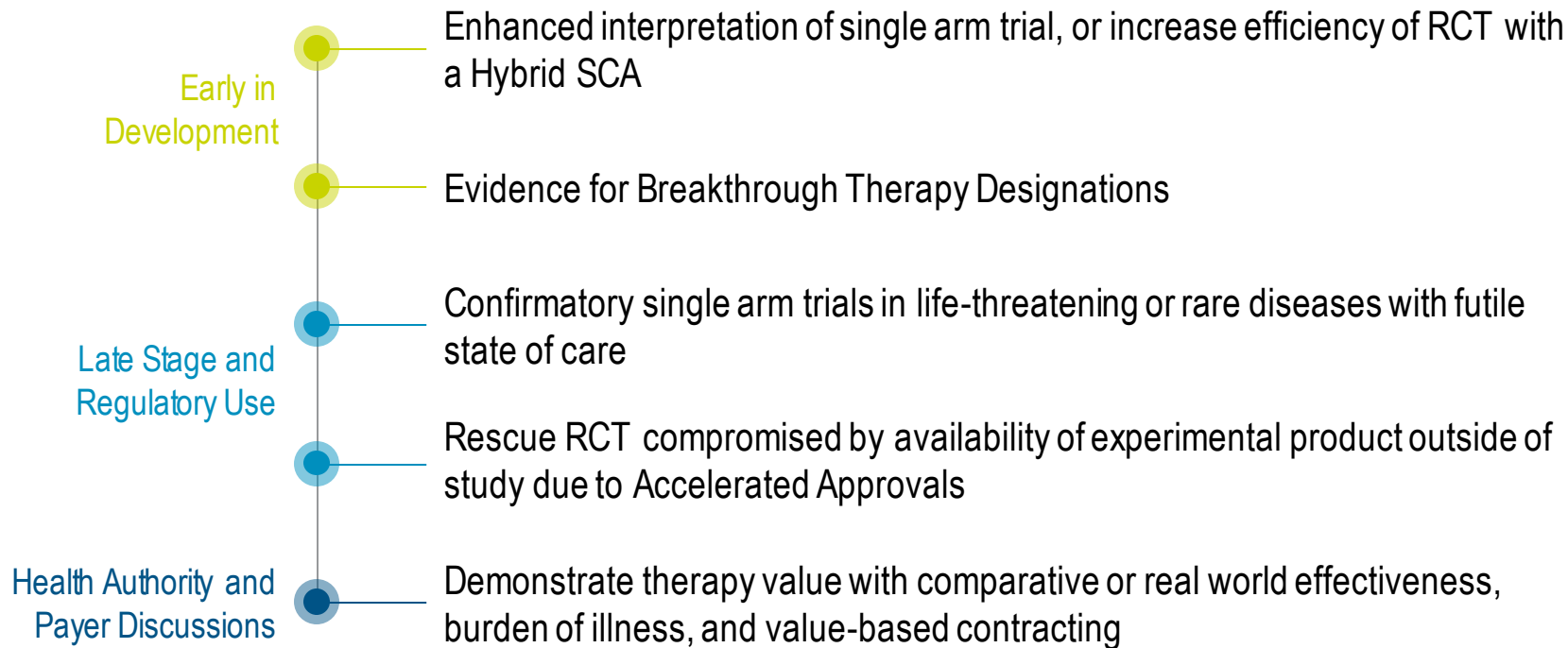
Synthetic Control Arm[®]

What is a Synthetic Control Arm[®]?

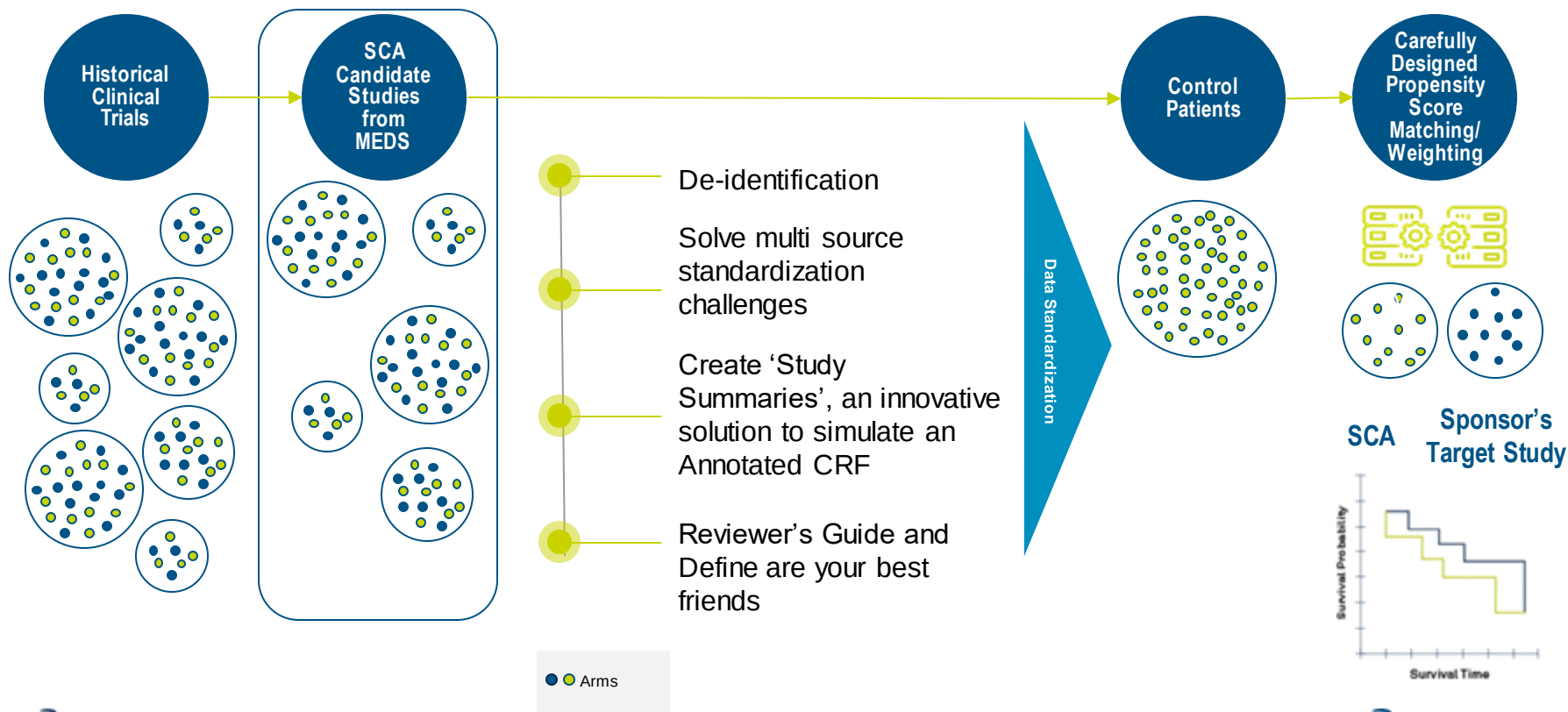
Employs **precise statistical matching** from a vast pool of patients in **past trial** to patients in the **experimental arm** of a current day clinical trial.



What are the typical applications of a Synthetic Control Arm®?



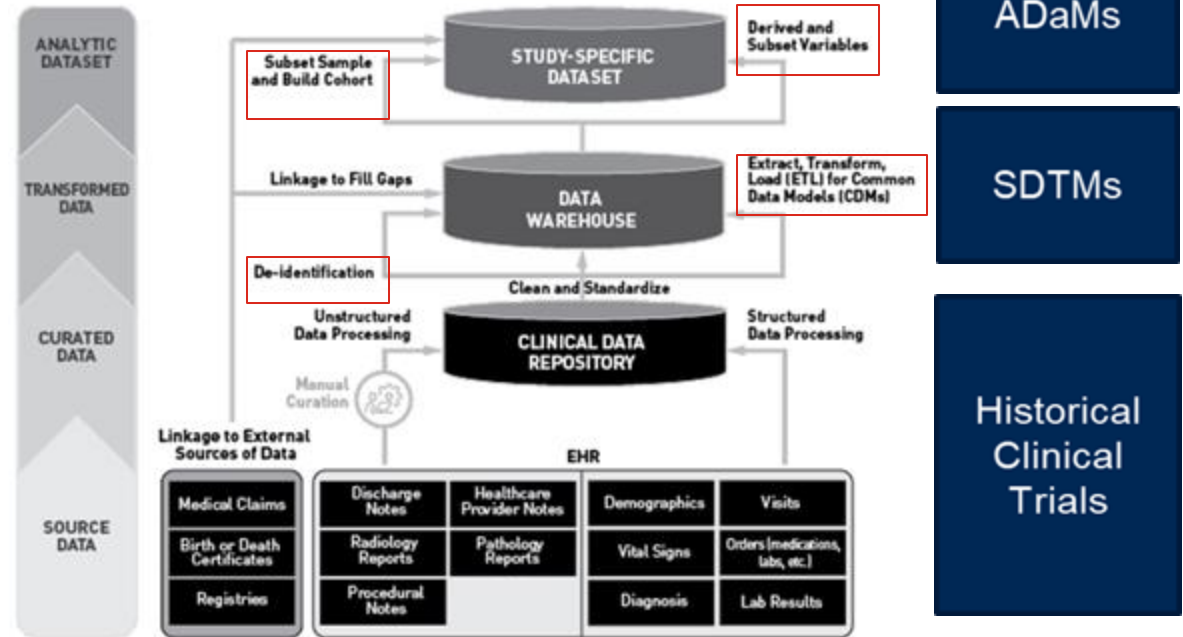
How we prepare data for a Synthetic Control Arm®



SCA Data Standardization Essentials

Milestones of HCT Data Transformation

Although HCT and RWD are poles apart in data Quality, they are not much different in Milestones of data transformation



FDA. (2021, September). *Guidance Document: Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products*. Retrieved February 10, 2023, from <https://www.fda.gov/media/152503/download>

Protect the privacy, at all costs

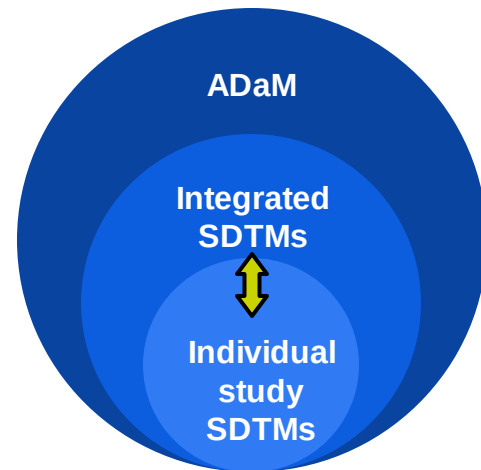
- De-identification is generally defined as the process by which personal identifiers are removed/masked from an individual's health information.
- It is an essential step for ethical use of Historical Clinical Trial data.
- We developed custom de-identification protocols with external privacy experts to aggregate data without compromising individual or sponsor privacy.

Multi-Source Challenges

The following flow of standardization is often streamlined and time efficient in a multi trial setup.

A long term vision of the Integrated SDTM datasets pays dividends at the ADaM Phase of your standardization.

- Organizational level standards
- Reactive codelists
- Non-standard variable consistency.



The Tabular eCRF- Study Summary Report

formId	FormName	FieldID	PreText	PostText	SDTM_Domain	SDTM_Variable	Condition	Not_Mapped_Reason
VIT	Vital Signs, Blood Pressure, Weight, Height (VIT)	SBP	Systolic blood pressure	mmHg	VS	VSORRES	VSTESTCD=SYSBP VSTEST=Systolic Blood Pressure VSORRESU=mmHg	
VIT	Vital Signs, Blood Pressure, Weight, Height (VIT)	DBP	Diastolic blood pressure	mmHg	VS	VSORRES	VSTESTCD=DIABP VSTEST=Diastolic Blood Pressure VSORRESU=mmHg	
VIT1	Vital Signs, Weight (VIT1)	SBP	Systolic blood pressure	mmHg	VS	VSORRES	VSTESTCD=SYSBP VSTEST=Systolic Blood Pressure VSORRESU=mmHg	
VIT1	Vital Signs, Weight (VIT1)	DBP	Diastolic blood pressure	mmHg	VS	VSORRES	VSTESTCD=DIABP VSTEST=Diastolic Blood Pressure VSORRESU=mmHg	

This Tabular eCRF is a great tool to provide a flavour of the data to Biostats during the Blinding phase.

It also serves as the precursor to the supporting documents requested in SDRG and Define-xml, as noted in the earliest FDA RWD data standards guidance.

2 Vital Signs Details	
2.1	Systolic Blood Pressure VSORRES when VSTESTCD=SYSBP
2.2	Systolic Blood Pressure Unit VSORRESN when VSTESTCD=SYSBP
2.3	Diastolic Blood Pressure VSORRES when VSTESTCD=DIABP
2.4	Diastolic Blood Pressure Unit VSORRESN when VSTESTCD=DIABP
2.5	Blood Pressure Position BP_VSPOS
	☐ Prone ☐ Semi-Recurrent ☐ Sitting ☐ Standing ☐ Supine VSPOS

Documentation of the sponsor's rationale for choosing particular CDISC data elements for RWD and documentation of the differences between the two is critical. The sponsor should provide a description of the general approach and anticipated impact of data mapping as a part of or in an appendix to the *Study Data Reviewer's Guide* to highlight the domains involved. Furthermore, the sponsor should include a data dictionary that documents the definition of every data element used and all relevant information about the element, such as its relationships to other data, origin, usage, and format. The technical details, best not included in the Study Data Reviewer's Guide,

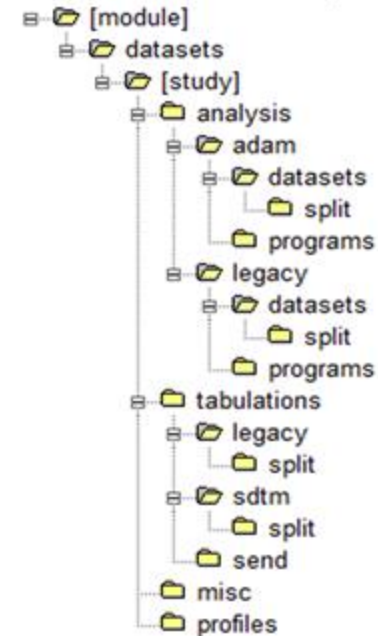
FDA. (2021, October). *Guidance Document: Data Standards for Drug and Biological Product Submissions Containing Real-World Data*. Retrieved February 10, 2023, from <https://www.fda.gov/media/153341/download>

RG, SDSP, Define-XML and Misc

Reviewer's Guides, SDSP and Define-XML are your new best friends, especially for a SCA submission.

Miscellaneous Folder is a great place to have your intermediary datasets, analysis programs and files that might not fit in the 'datasets' and 'tabulations' folders

Figure 1: Folder Structure for Study Datasets



FDA. (2022, October). STUDY DATA TECHNICAL CONFORMANCE GUIDE. Retrieved February 10, 2023, from <https://www.fda.gov/media/153632/download>

Applications of SCAs in Medical Product Development

Applications of SCAs in Medical Product Development

Early in Development

A SCA was created for the Immunon's Phase Ib OVATION I trial resulting in fast track designation from the FDA.

Late Stage and Regulatory Use

A SCA was used to demonstrate efficacy in Medicenna's single-arm Phase II trial in Recurrent Glioblastoma. After a positive discussion of the design at the end-of-Phase 2 meeting, Medicenna plans to use a hybrid SCA in a Phase III study.

Health Authority and Payer Discussions

A SCA was built for single arm trial in R/R B-ALL trial demonstrated clinically relevant improvement of overall complete remission at 24 months and overall survival.

Research and Collaborations

Research Collaboration Agreement with Pediatric Review Committee (PeRC) at the FDA explored using the Synthetic Control Arm approach to aid in adult-to-pediatric extrapolation decisions

Friends of Cancer Research Synthetic Control Arm® Case Study in Non-Small Cell Lung Cancer and Multiple Myeloma

Synthetic Control Arm References

- Historic Clinical Trial External Control Arm Provides Actionable GEN-1 Efficacy Estimate Before a Randomized Trial [Paper](#)
- Building an External Control Arm for Development of a New Molecular Entity: An Application in a Recurrent GBM Trial for MDNA55 [Paper](#)
- Utility of propensity score-based Bayesian borrowing of external adult data in pediatric trials: A pragmatic evaluation through a case study in acute lymphoblastic leukemia (ALL) [Paper](#)
- Exploring the Potential of External Control Arms created from Patient Level Data: A case study in non-small cell lung cancer [Paper](#)

