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Transforming Rare Disease Trials with Synthetic Control Arm®

Bhargav Koduru and Corinne Ahlberg

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Introductions

Bhargav Koduru

Senior 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

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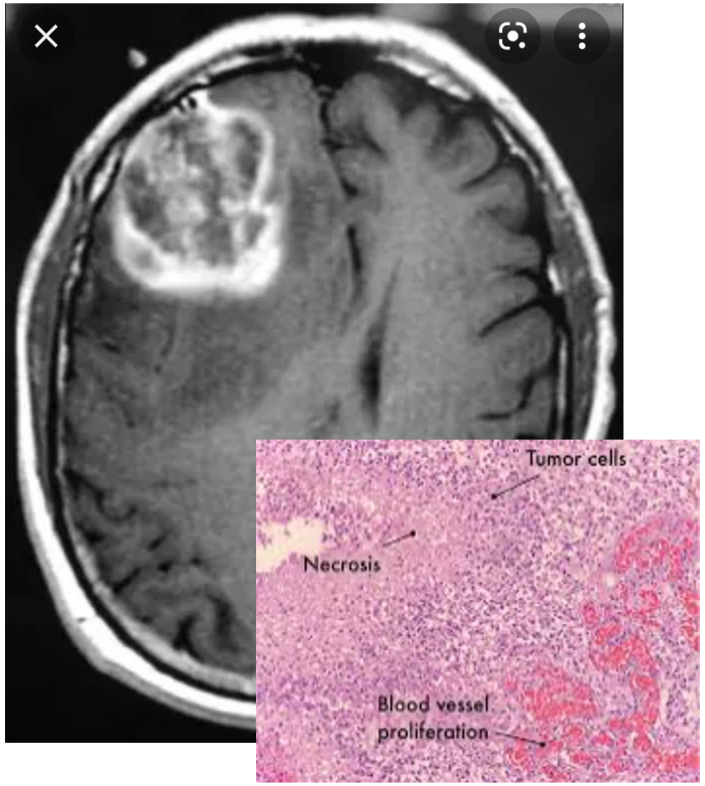
Recurrent Glioblastoma

Recurrent Glioblastoma Overview



- Rare cancer **<2% of all cancer patients** are primary brain tumors
- Most common primary brain tumor with **~13,000 people diagnosed annually**
- Incurable rapidly fatal cancer with substantial morbidity
  - 5-year survival <5%
  - At recurrence median survival time **~ 6-9 months**
- No known therapies prolong life after recurrence
- Median age at diagnosis 64 years
- Possible options:
  - Local therapies for local symptom management include repeat surgery and/or re-irradiation
  - Angiogenesis Inhibitors, Chemotherapy and TRK inhibitors (If actionable mutation observed)
  - US guidelines recommend **systemic therapy on a clinical trial** to improve quality of life.

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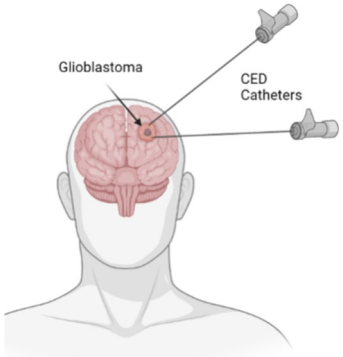
Synthetic Control Arm: A game changer for GBM.



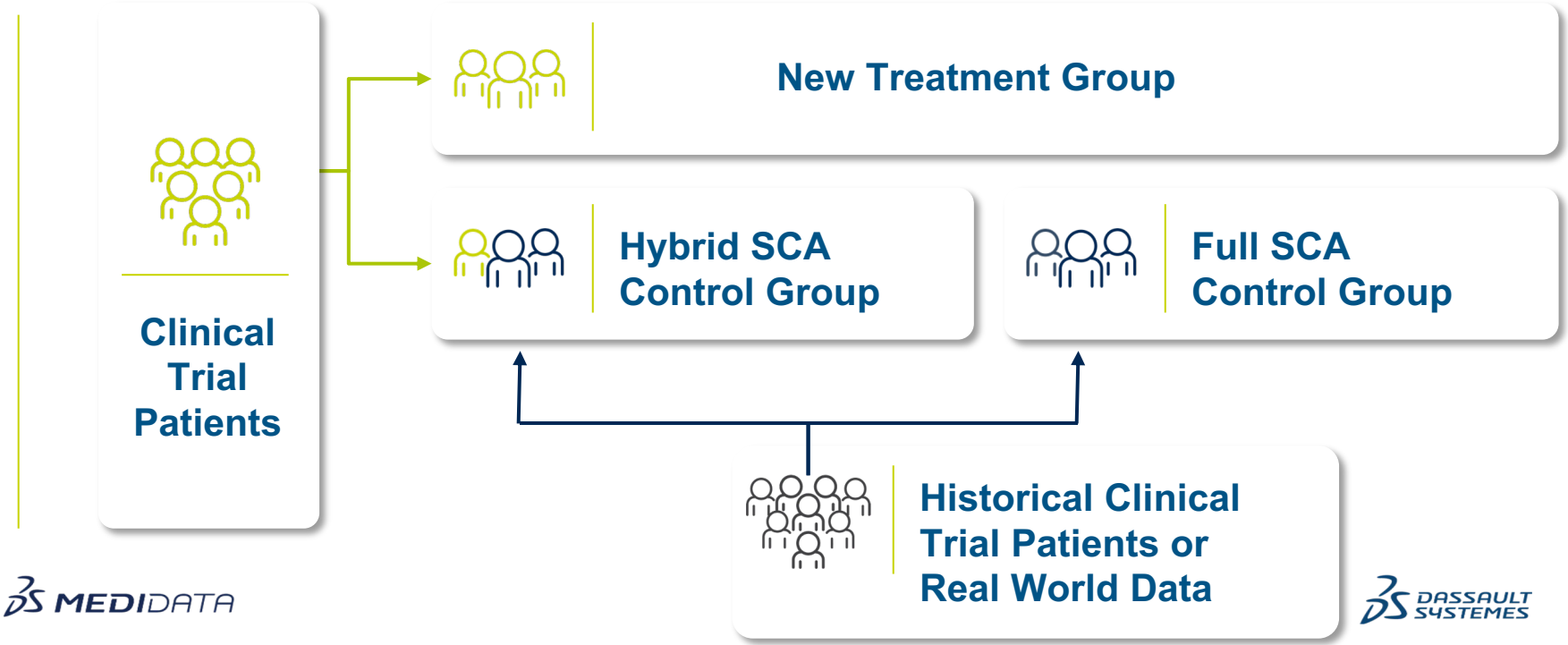
- **Better Patient Selection:** SCAs enable the selection of a patient population with well-defined characteristics
- **Improved Survival Assumptions:** With patient match on prognostic factors, synthetic control arms provide a more accurate median survival rate.
- **Efficiency in Recruitment:** Given the rarity and severity of glioma, recruiting a sufficiently large and well-defined patient population for traditional control arms is challenging.
- **Ethical Considerations:** Providing the investigational drug to all trial participants is more ethical for diseases with poor prognosis like glioma.

https://www.clinicalleader.com/doc/how-an-external-control-arm-changed-phase-trials-for-brain-cancer-0001

Synthetic Control Arm®

What is a Synthetic Control Arm®?

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



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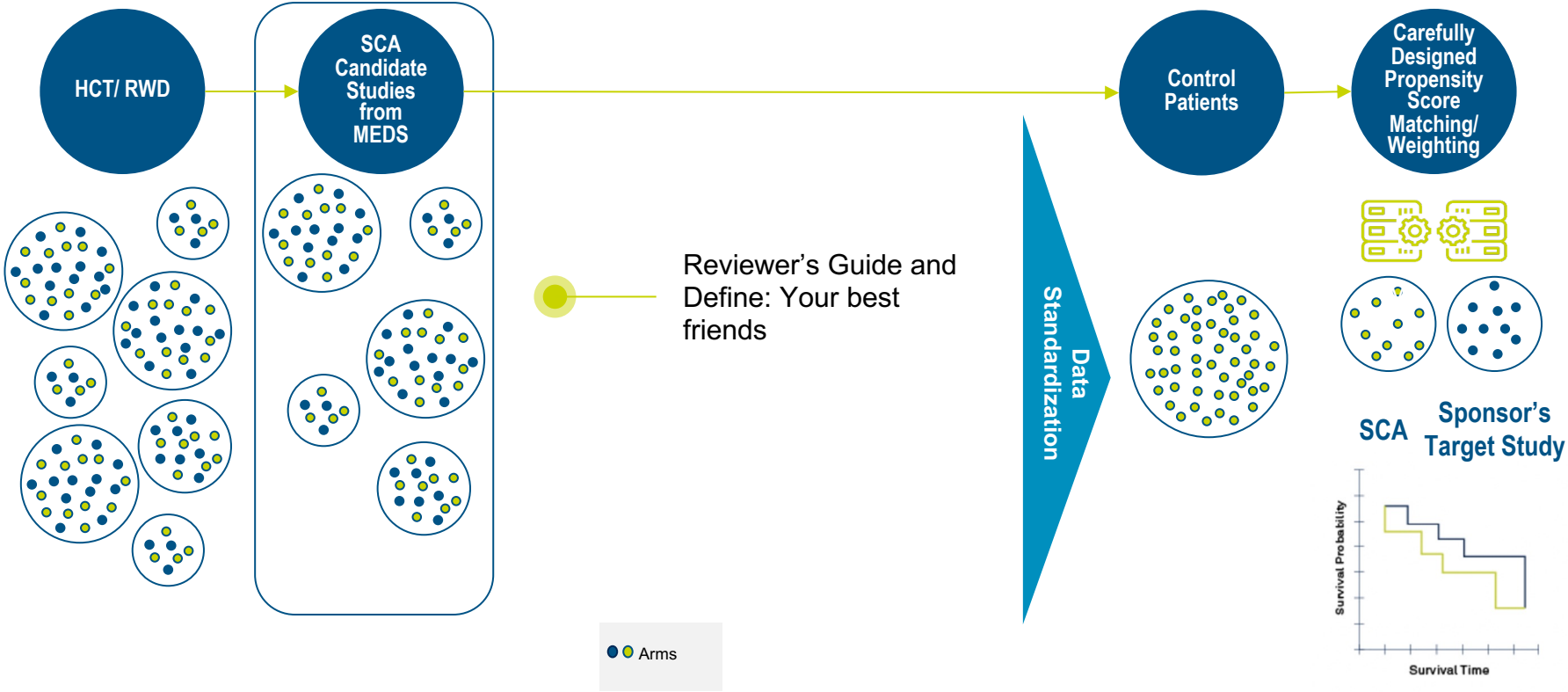
How we prepare data for a Synthetic Control Arm®



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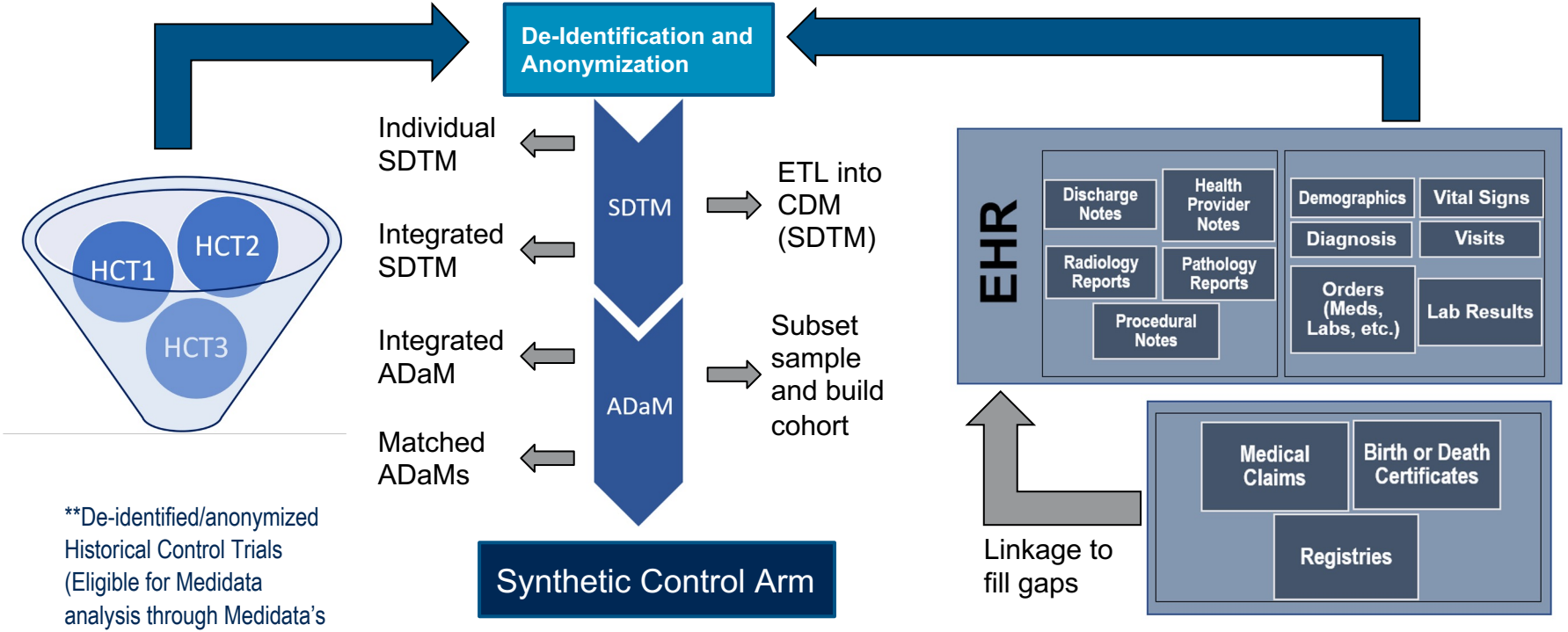
Data Standardization Strategy

Milestones of Data Transformation



**De-identified/anonymized Historical Control Trials (Eligible for Medidata analysis through Medidata's data collaboration program).

Adopted from 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

iADRG and Misc

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,

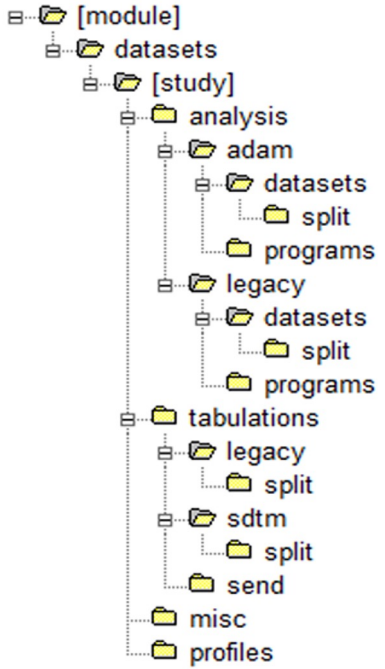
FDA. (2021, October). Guidance Document: Data Standards for Drug and Biological Product Submissions Containing Real-World Data. Retrieved February 10, 2023, from https://www.fda.gov/media/153341/download

- 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
- Use the iADRG for summarizing your data definitions/derivations and approach to analysis data in general

https://advance.phuse.global/pages/viewpage.action?pageId=80806990

New

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

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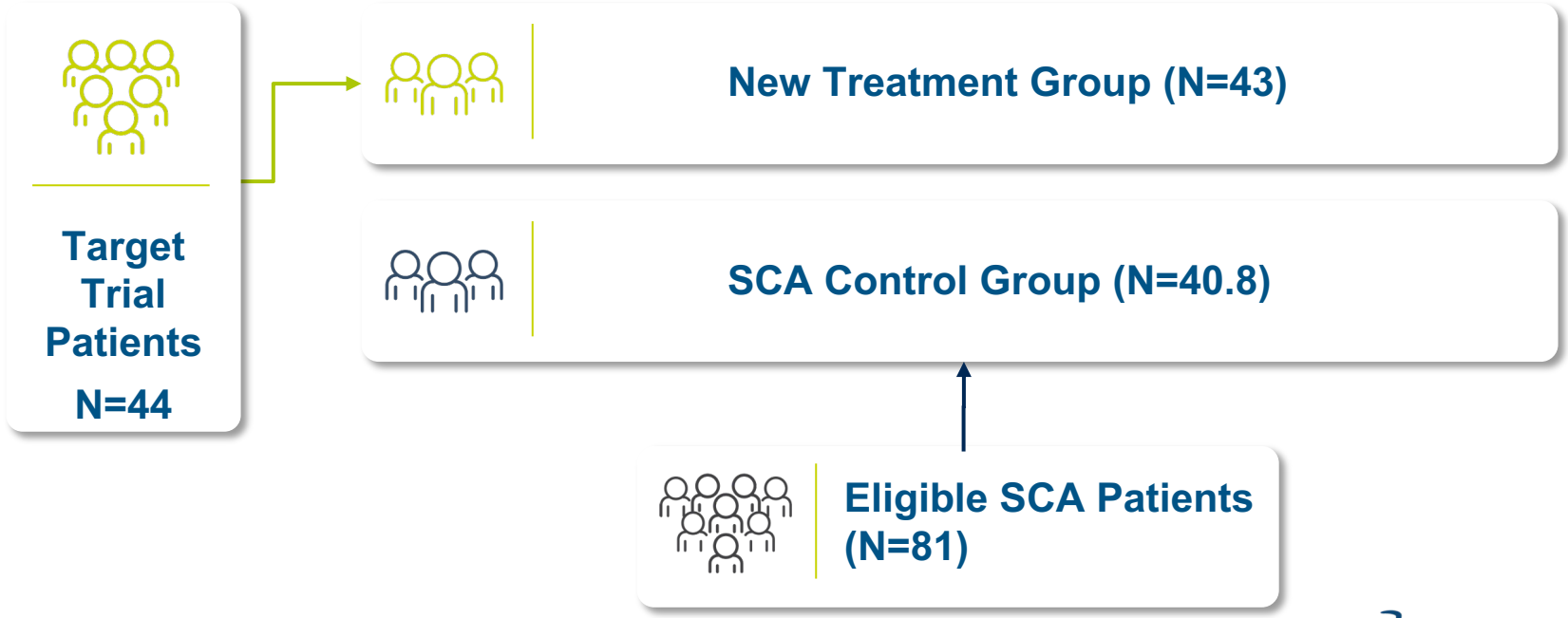
Applications of SCA in Recurrent Glioblastoma

Phase 2 Study Design

An open-label, non-randomized, Phase 2, multicenter study of Convection-Enhanced Delivery (CED) of MDNA55 in adults with recurrent or progressive Glioblastoma



ClinicalTrials.gov ID#: NCT02858895

Overview of Propensity Score Matching

Before Propensity Score Matching

Target Trial Patients

Eligible SCA Patients

After Propensity Score Matching

Target Trial Patients

SCA Patients

Overview of Propensity Score Weighting

Before Propensity Score Weighting

Target Trial Patients

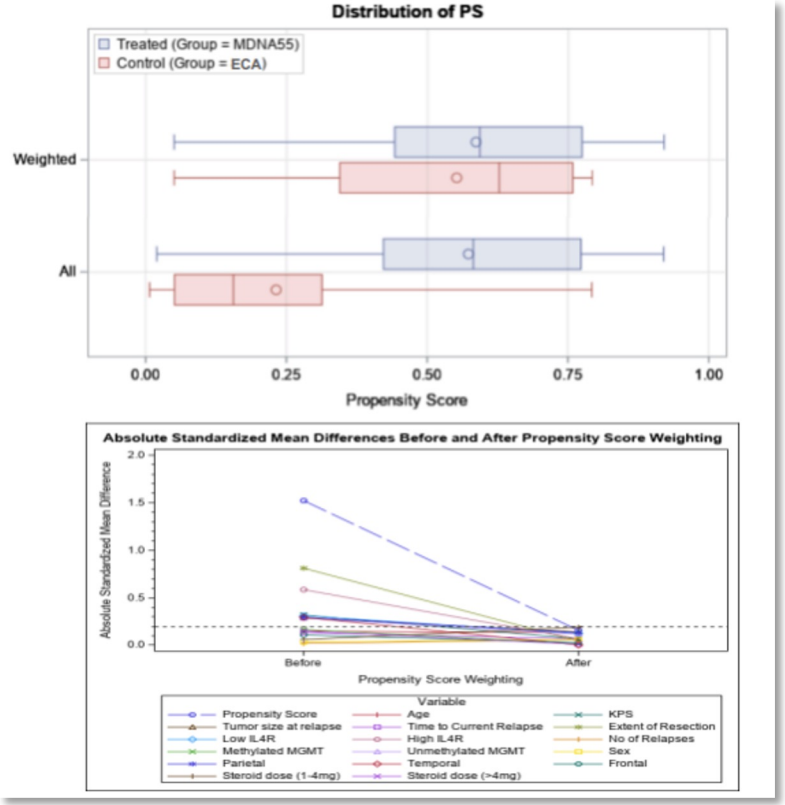
Eligible SCA Patients

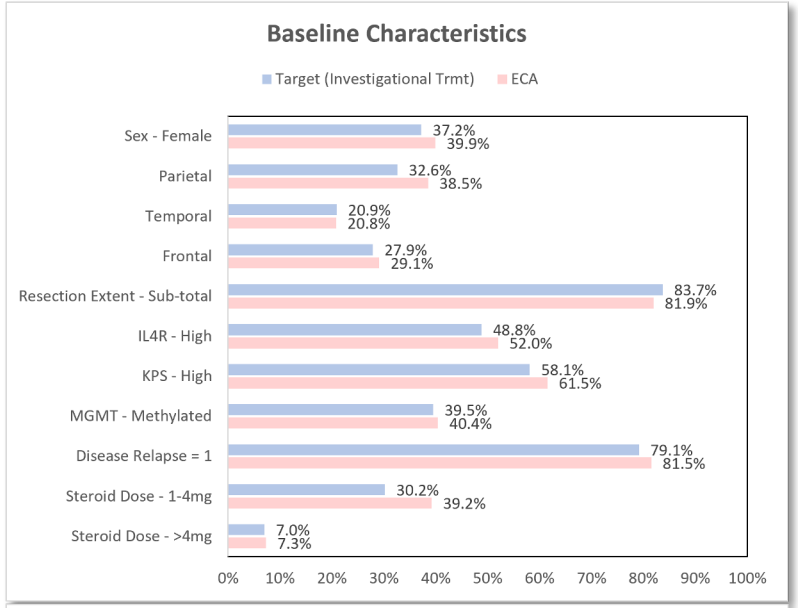
After Propensity Score Weighting

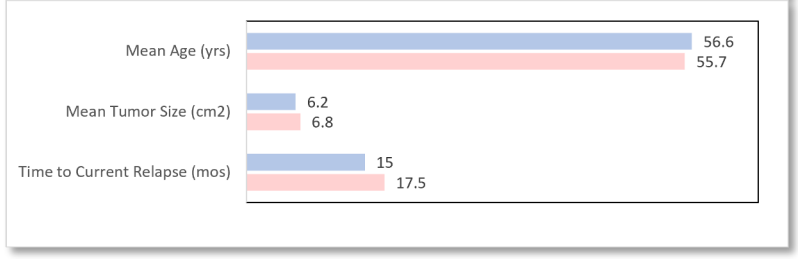
Target Trial Patients

SCA Patients

Phase 2 SCA PS Weighting Results







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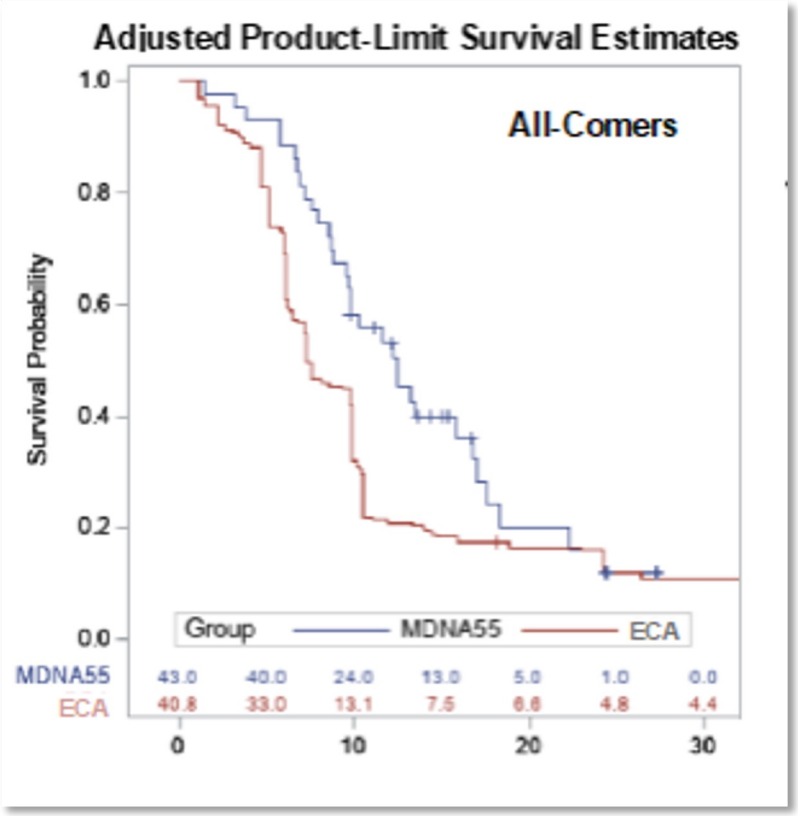
Phase 2 Overall Survival Results



Propensity score weighted estimates:

Group	Median (months)	Log-rank test p-value
MDNA55 (n=43)	12.4	0.1426
ECA (n=40.8)	7.2	

Comparison	Hazard Ratio	95% Confidence Limits	
MDNA55 vs ECA	0.634	0.392	1.026

- Quantified treatment effect of 37% risk reduction of death was considered clinically meaningful
- A GO decision to full development was made
- Registrational trial with a hybrid ECA was planned

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Majumdar, A., Davi, R., Bexon, M. et al. Building an External Control Arm for Development of a New Molecular Entity: An Application in a Recurrent Glioblastoma Trial for MDNA55. Stat Biosci 14, 285–303 (2022). https://doi.org/10.1007/s12561-022-09337-7

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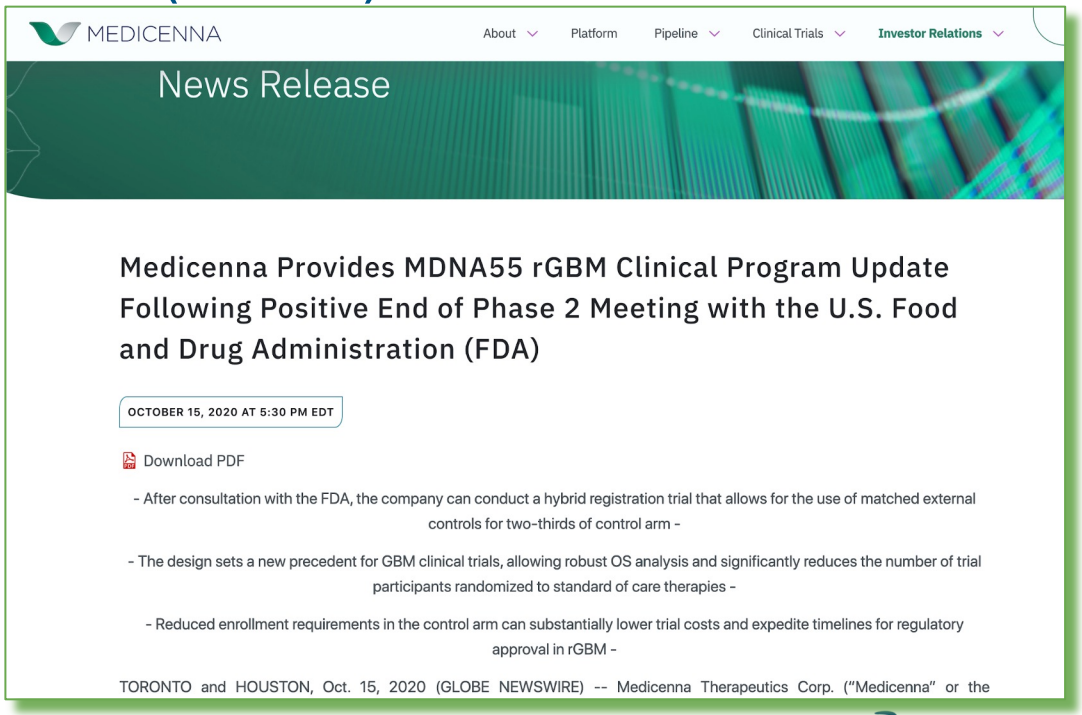
FDA Agrees to Synthetic Control Arm® Design in Recurrent Glioblastoma (rGBM)

- For the first time, the **FDA approved the use of hybrid Synthetic Control Arm (SCA) in a Phase III study design in rGBM**
- Medicenna used a Medidata SCA to demonstrate efficacy in a single-arm Phase II trial, with the goal of **using the results to design a Phase 3 SCA-based registrational trial**
- **The SCA demonstrated large efficacy effect size** in all-comers subjects, as well as in subjects expressing high levels of IL4R.



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About Platform Pipeline Clinical Trials Investor Relations

News Release

Medicenna Provides MDNA55 rGBM Clinical Program Update Following Positive End of Phase 2 Meeting with the U.S. Food and Drug Administration (FDA)

OCTOBER 15, 2020 AT 5:30 PM EDT

Download PDF

- After consultation with the FDA, the company can conduct a hybrid registration trial that allows for the use of matched external controls for two-thirds of control arm -

- The design sets a new precedent for GBM clinical trials, allowing robust OS analysis and significantly reduces the number of trial participants randomized to standard of care therapies -

- Reduced enrollment requirements in the control arm can substantially lower trial costs and expedite timelines for regulatory approval in rGBM -

TORONTO and HOUSTON, Oct. 15, 2020 (GLOBE NEWSWIRE) -- Medicenna Therapeutics Corp. ("Medicenna" or the

https://ir.medicenna.com/news-releases/news-release-details/medicenna-provides-mdna55-rgbm-clinical-program-update-following

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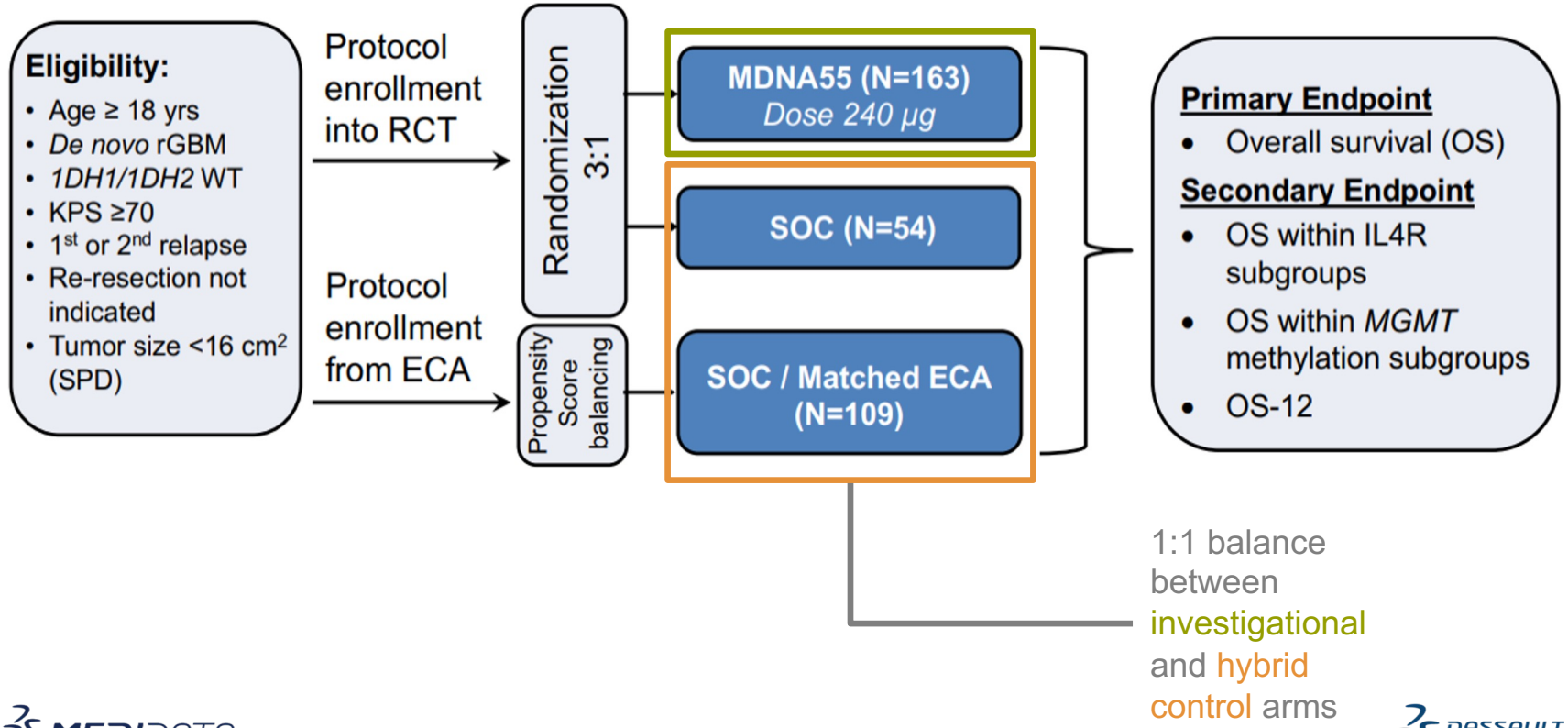
Planned Phase 3 Trial - Hybrid Control Design



https://ir.medicenna.com/events/event-details/2020-society-neuro-oncology-sno-annual-meeting

Thank you

We represent a fantastic group of statistical programmers, SDTM SMEs and Biostatisticians at Medidata AI.

A special thanks to Lisa Ensign and Elizabeth Lamont for their help on the slides.

Medicenna for putting the trust in us to help them with finding a better cure for the rGBM community.

Countless patients who have made this data possible.