CDDF Multi-StakeHolder Workshop
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Synthetic and external arms

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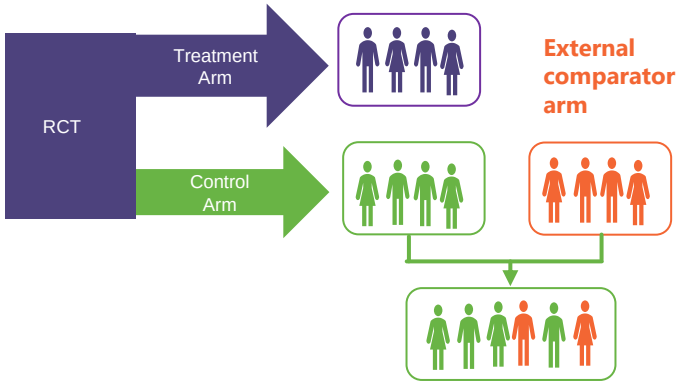
Disclaimer

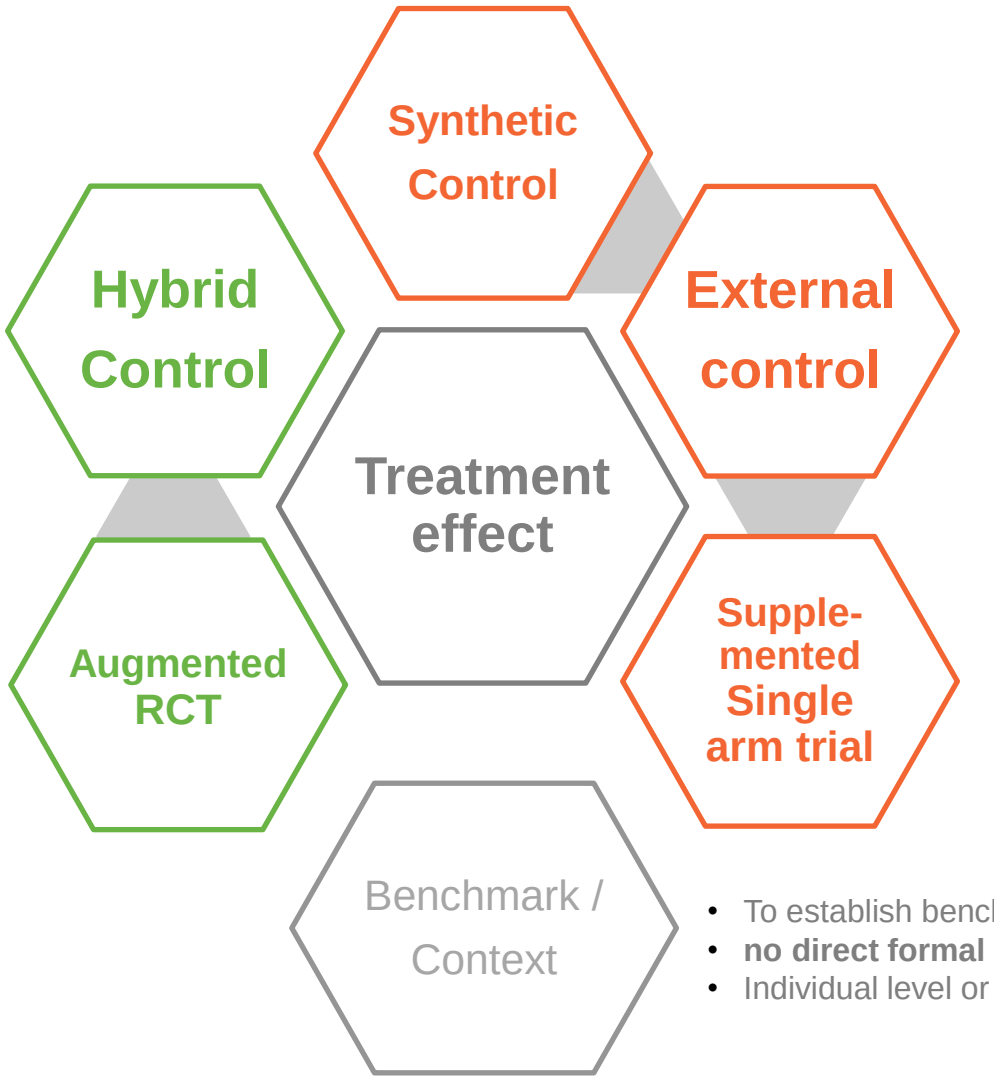
- GSK employee

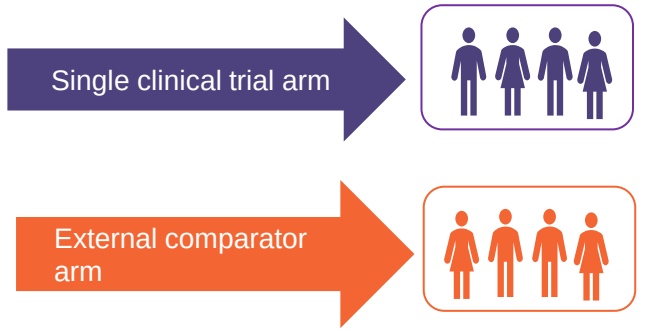
What is an External Control Arm (ECA)?

An **alternative to a trial internal control arm** constructed from **data collected from sources outside of the target trial**



- **Treatment effect estimation**
- Individual patient data needed
- Allows some assessment of similarity of ECA to internal control arm

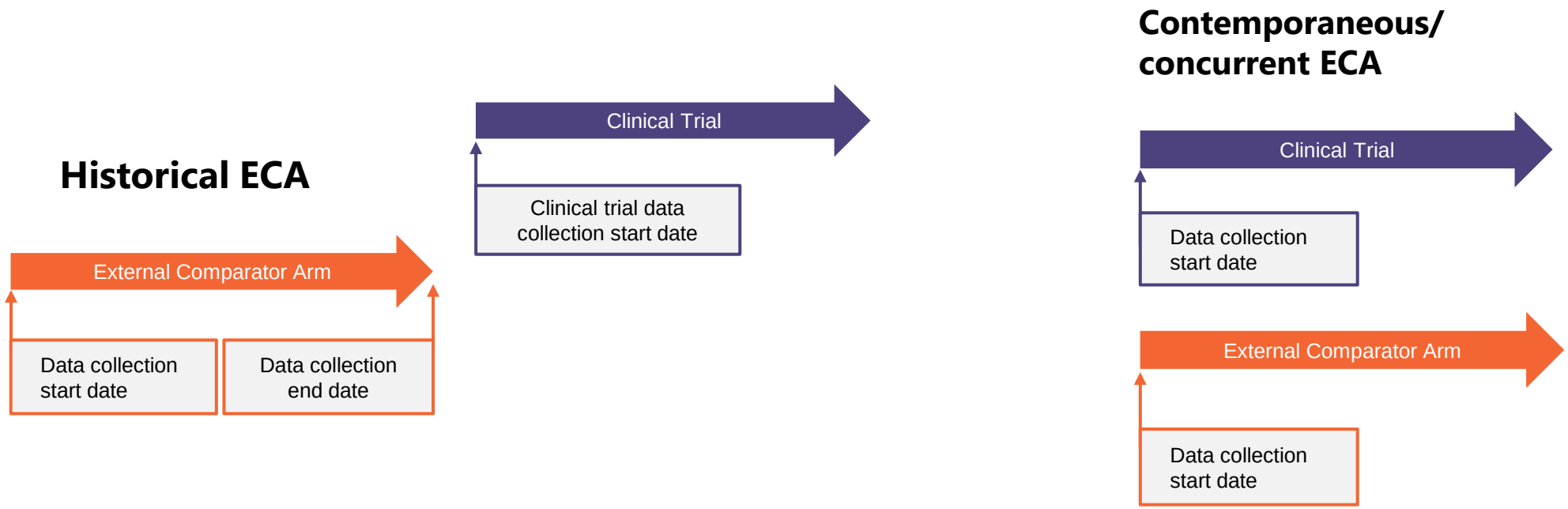




- **Treatment effect evaluation**
- Statistical adjustments to **limit** bias
- Individual patient data needed
- **Focus of FDA guidance on ECA**

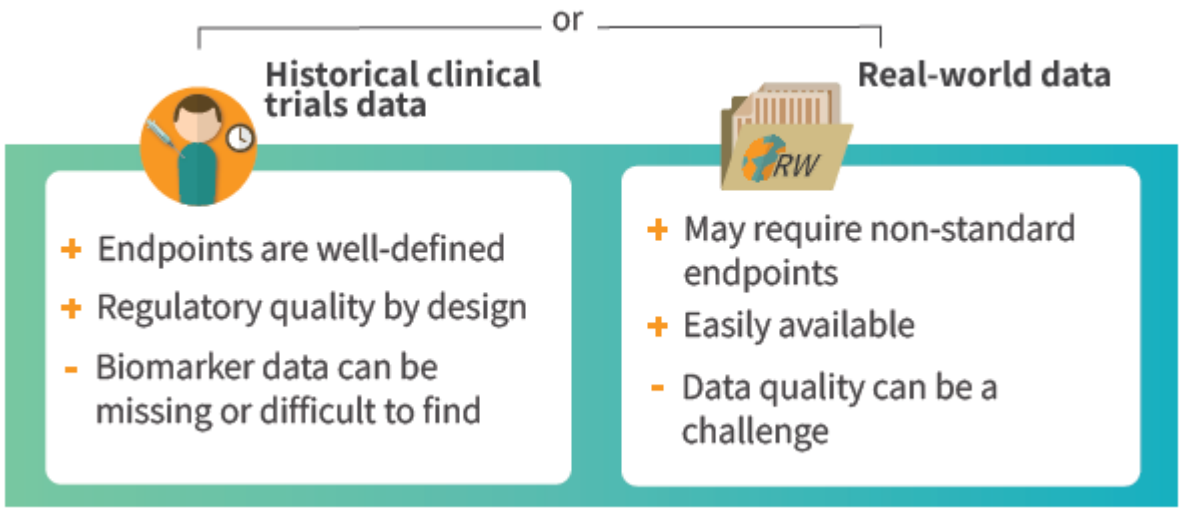
- To establish benchmark for **single arm trial**
- **no direct formal statistical comparison**
- Individual level or aggregate data can also be used

Types of ECA based on data collection timing



A mixed approach can also be implemented that involves collecting data both retrospectively (historical data) and prospectively (concurrent data).

ECA data sources



Sponsor own data

Project Data Sphere

TransCelerate BIOPHARMA INC.

Vivli CENTER FOR GLOBAL CLINICAL RESEARCH DATA

ClinicalStudy DataRequest.com

Drug surveillance data

Patient generated data

Registries

Claims

Omics data

Electronic medical records

Prospective cohorts

Linked resources

Bespoke curation of retrospective RWD

ECA uses and stakeholders

Sponsor

- to inform go/no-go decisions in early development

Regulatory authorities

- Contribution of components
- Supportive evidence of effect
- Primary evidence of effect: (New indication, Line/label extension, Confirmatory trial)
- Post marketing studies

Payers

- Cost-effectiveness
- Value proposition

When can a fully ECA be considered an option?

RCTs are unethical or unfeasible or lack equipoise

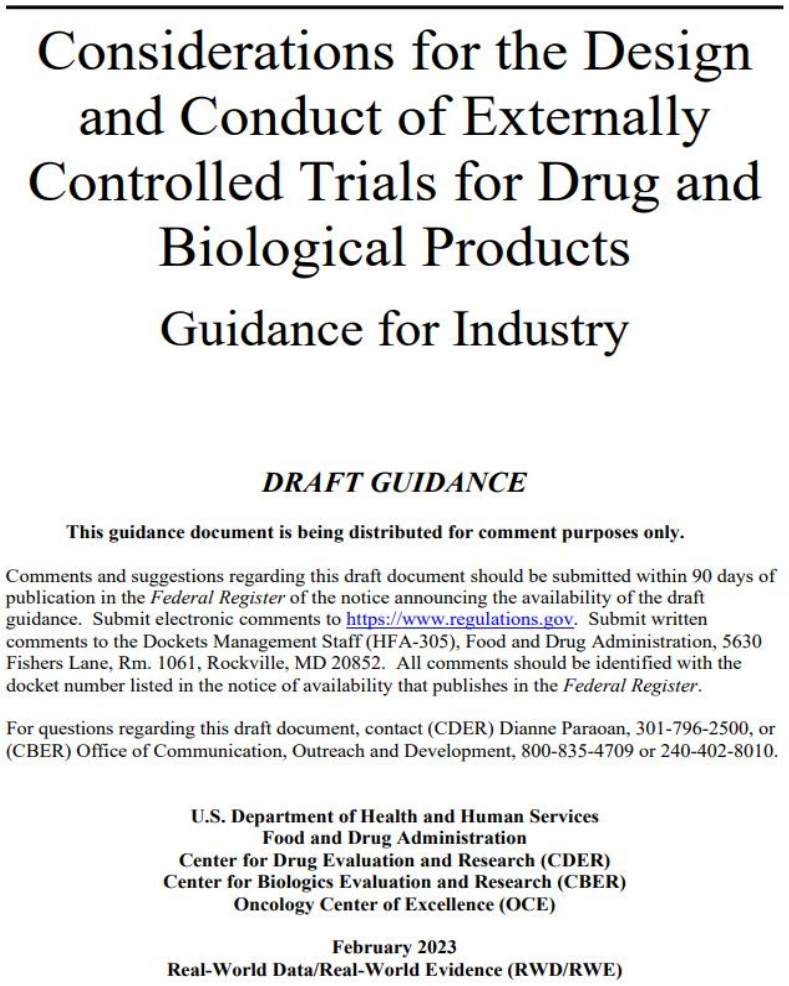
Not just “difficult”

- Rare indications / molecular subgroups
- Significant unmet medical need, limited treatment options
- Pediatrics
- Large treatment effect
  - unaffected by patient or physician motivation for treatment
  - causal relationship to treatment established
- Disease course is well understood, and standard of care has remained stable/predictable
- Outcome can be measured with minimum bias
- Prognostic factors of outcome well characterized

Source: Jahanshahi, M.,. et al. Ther Innov Regul Sci 55, 1019–1035 (2021).

FDA draft guidance on externally controlled trials

(Covers only fully external control arms)



Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dianne Paraoan, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

February 2023
Real-World Data/Real-World Evidence (RWD/RWE)

- Clear objective, target comparison and estimand
- Fit for purpose data sources “exchangeable ECA”
- Detailed a priori protocol including sample size justification
- Detailed a priori statistical analysis plan
- Early interactions with Agencies
- Access and Quality of source data

When are data fit for purpose?

Pembrolizumab and lenvatinib for patients with endometrial cancer not MSI-H/dMMR

FDA accelerated approval 2019
Breakthrough designation 2018*
FDA project ORBIS

Phase Ib/II basket
Study 111/Keynote 146
N=94

ORR 38.3% (95% CI, 28.5%-48.9%)
10 complete responses (10.6%)
25 patients with DOR>6m

2 ongoing RCT in 1L and 2L

ECA for contribution of components

Data from 3 former monotherapy clinical trials

Exploratory analyses included

- unadjusted cross-trial comparisons, which indicated a numerical improvement in ORR with the combination therapy as compared to each of the individual. (Sponsor)
- propensity score adjusted analyses provided consistent results (FDA) – limited to covariates measured in all 4 studies
- Results supported the application

Arora S, et al. Clin Cancer Res. 2020;26(19):5062-5067. * for renal cell cancer and this indication

Axicabtagene Ciloleucel (Yescarta) for the Treatment of Diffuse Large B-Cell Lymphoma

EMA approval 2018 for DLBCL
Orphan indication, Priority medicine
FDA approval 2017 not using ECA

ZUMA-1 phase II (NCT02348216)

DLBCL (76%), TFL (16%), PMBCL (8%)

ORR (ICR) : 66% (95%CI 56%–75%)
at median follow-up 15.1 months
CR rate : 47%
median DOR 14.0 (0.0–17.3)

ECA for supportive evidence of efficacy (EMA)

SCHOLAR-1, companion study to ZUMA 1:

- Retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (n = 636) - 60% from 2 past RCT studies, 40% from Mayo&MD Anderson cancer center.
- Patients who had PD/SD to last line of therapy and relapsed within 12 months, ECOG PS 0-2 and baseline within 3m of relapse.
- The difference for CR between SCHOLAR-1 (CR; 11.5%) and ZUMA-1 (CR; 47%) was 35.5% using ITT and central review **considered beyond any chance finding, supported approval by EMA**

DLBCL: diffuse large B-cell lymphoma , TFL: transformed follicular lymphoma, PMBCL: primary mediastinal B-cell lymphoma

Papadouli I et al. Oncologist 2020 Oct;25(10):894-902. doi:10.1634/theoncologist.2019-0646. Epub 2020 Apr 27.

Blinatumomab for patients with precursor B-cell acute lymphoblastic leukemia in first or second complete remission with detectable minimal residual disease (MRD, ≥0.1%)

Label extension (2018)
approved 2017
(Ph(-) relapsed/refractory BCP ALL)

FDA Orphan indication

BLAST study (MT103203)
single arm, multicenter phase II
N=87 patients with MRD

Complete MRD response:
79% (95% CI: 70%, 88%).

median RFS 22.3 months.

ECA for supportive evidence of efficacy

- ECA derived from retrospective non US cohort study 2120148.
- Propensity matching on baseline patient clinical characteristics and by time from MRD measurement to start of therapy or relapse, and Inverse probability of HSCT weighting
- Numerical advantage for RFS, no advantage on OS
- Caveats → information regarded as exploratory
  - Matching resulted in reduction of sample size by 1/3
  - Residual confounding (rates of HSCT and subsequent treatment)
  - Temporal differences in the data
  - Differential follow-up

HSCT: hematopoietic stem cell transpantation, IPTW: inverse probability of treatment weighting, BCP ALL= b-cell positive acule lymphoblastic leukemia, ALL: Acute lymphoblastic leukemia, Ph(-) = philadelphia negative

Jen EY et al. Clin Cancer Res Clin Cancer Res; 25(2) January 15, 2019

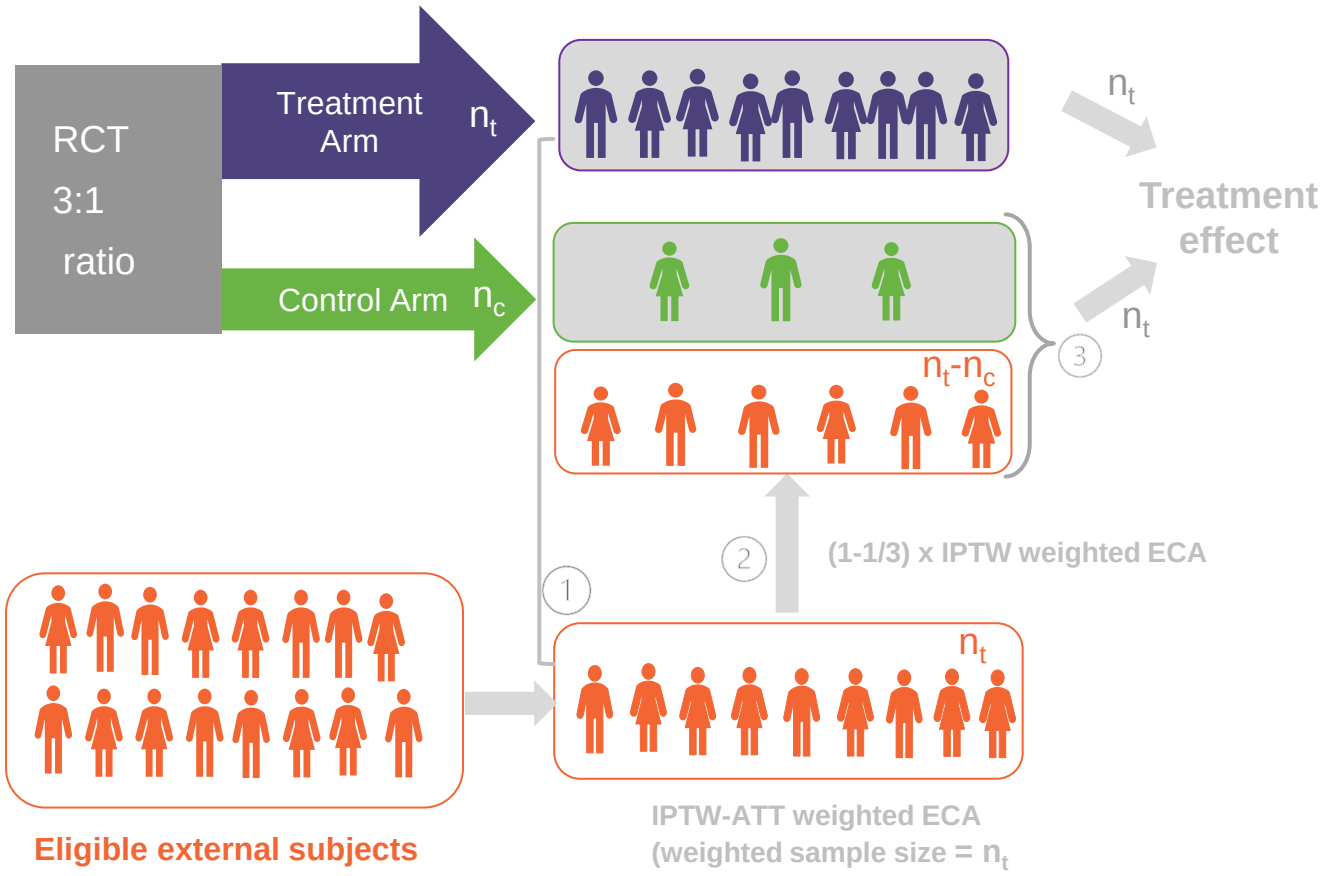
Hybrid control arm for a phase II study in rGBM

MDNA55 for recurrent GBM
(interleukin 4 receptor (IL4R)-targeting toxin)
Fast track / Orphan

Phase II single arm (n=43, 2017-2019)
+
Retrospective ECA from registry with IL4R positive patients (N=62, 2011-2019)
→ Supportive of benefit on OS
(from treatment start)

Registrational phase III using hybrid control arm supported by FDA

ECA for evidence of efficacy (Phase III registrational)



.Majumdar et al *Stat Biosci*. 2022**14**(2):285–303. Sampson JH et al Neuro Oncol. 2023 Jun; 25(6): 1085–1097
Medicenna Provides MDNA55 rGBM Clinical Program Update (globenewswire.com).

External control arms

- Not a low burden effort
  - Convincing rationale that a RCT is not feasible
  - Large high quality & complete databases
  - High burden to demonstrate that the ECA meets the bar for valid treatment comparison
- Strong design and analytical plan required
  - Analytic methods cannot eliminate the threat of bias completely
  - Strong assumptions are required, sensitivity analyses to assess robustness of results to assumptions
- **Hybrid randomized** designs may provide more robust results in the future
- Sufficient evidence of safety is also required