Developing Fit-for-Purpose External Control Arms to Optimize Submissions to Regulatory and Health Technology Assessment Agencies

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Our Speakers

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Jen Wogen has more than 20 years of experience in the design and conduct of retrospective and prospective studies across epidemiology, health economics, outcomes research, and health services research, including external control arm studies. Jen has an MS in Epidemiology from the University of Texas.

Craig Parzynski, MS
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Craig Parzynski has 17 years of experience in research and statistical analysis. He has contributed to over 40 peer-reviewed journal articles in observational and real-world evidence studies including external control arms. Craig has an MS in Biostatistics from the University of Pittsburgh.

Learning Objectives

- Describe the framework for using real-world data (RWD) to enable a comparison group for a single-arm clinical trial.
- Understand key regulatory and HTA agency concerns regarding methodological challenges to ECAs.
- Explore the pathways to early engagement with regulatory and HTA agencies to assess the suitability of ECA methods to complement a clinical trial program in support of drug approval.

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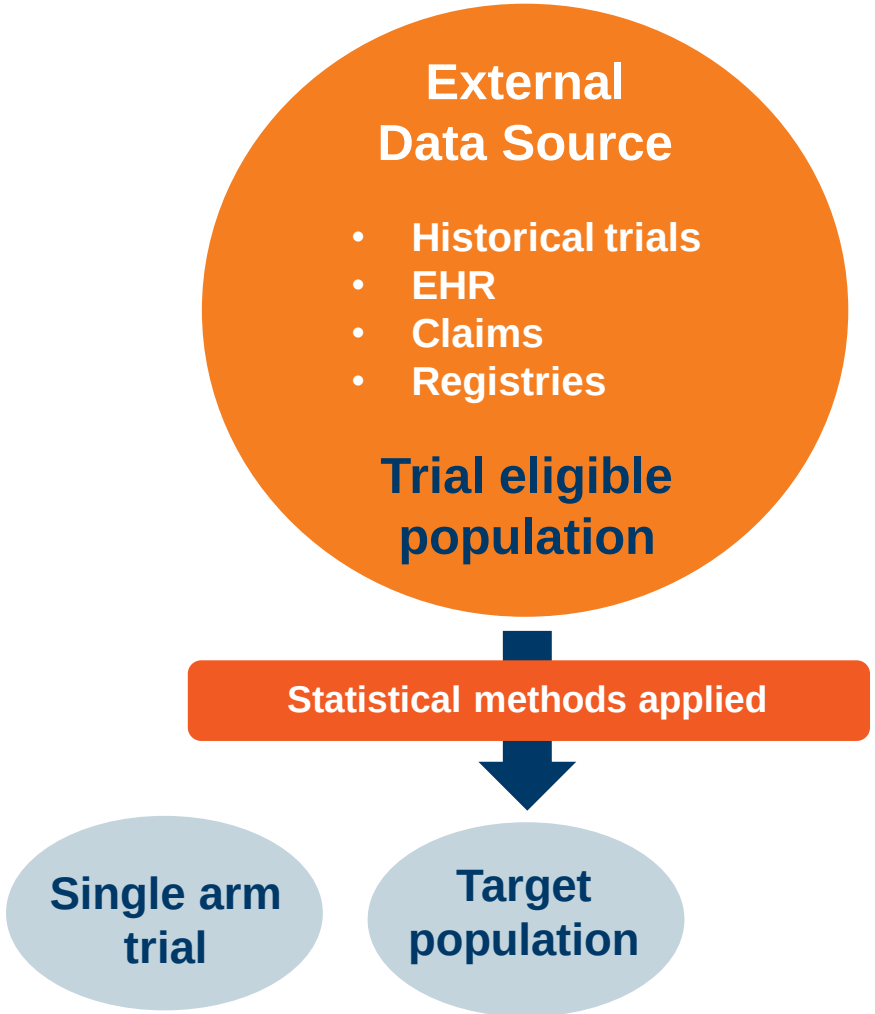
What is an ECA and when are they used?



When are they used?

- To contextualize single-arm trial data (efficacy comparison, benchmark).
- Where it is not feasible or ethical to use a placebo.
- When the standard of care is likely to be updated during the course of the study.
- For rare disease and oncology therapeutic areas.

Target population receiving standard of care or physician's treatment choice is used as ECA.

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U.S. Food Drug Administration. Center for Drugs Evaluation Research. February 2023. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry. Rockville, MD.

The FDA has outlined key early considerations when designing an ECA

- ✓ Incorporate ECA as part of the **overall clinical trial program** development.
- ✓ **Straightforward approaches** are better than complex ones with many assumptions.
- ✓ Target **trial emulation**.
- ✓ Select the optimal RWD source via **feasibility assessments**:
  - Inclusion criteria application
  - Comparable endpoints
  - Prognostic variables
  - Assess the extent of **missingness**

✓ Ensure **comparability** between the trial and EC arms:

- Time periods
- Patient demographics
- Prognostic factors
- Diagnostic criteria
- Treatments
- Other treatment-related factors
- Intercurrent events
- Endpoints

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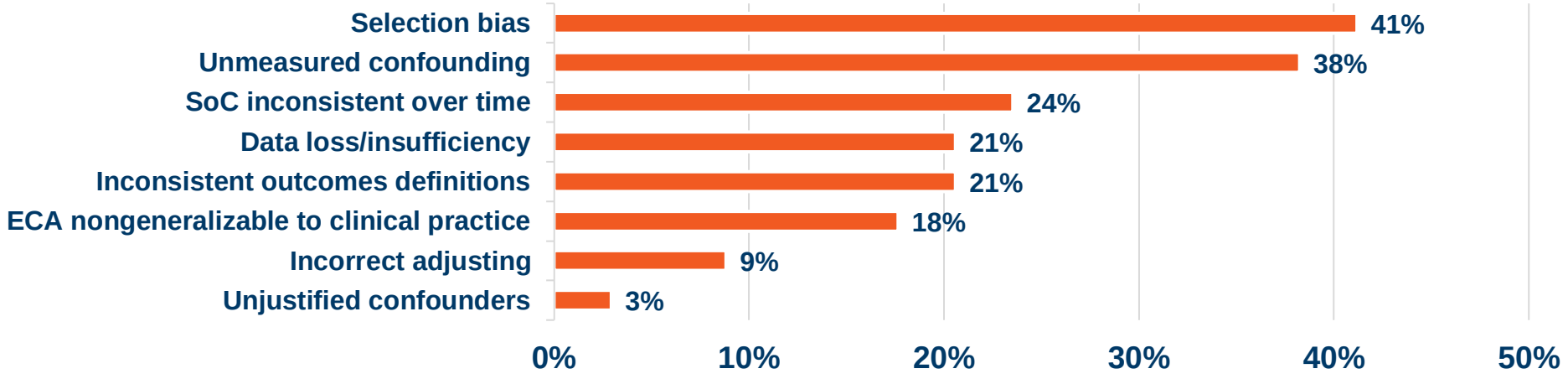
U.S. Food Drug Administration. Center for Drugs Evaluation Research. February 2023. Considerations for the Design and Conductof Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry. Rockville, MD.

Discordant critical feedback from regulatory and HTA agency review

	Regulatory Review			HTA Review		
	# Reviews	% High Influence	Mean # Critiques/Review	# Reviews	% High Influence	Mean # Critiques/Review
Blinatumomab Ph- ALL	3	67%	1.0	5	20%	2.0
Blinatumomab MRD+ ALL	3	0%	1.0	4	25%	2.3
Avelumab	3	0%	0.7	5	40%	0.8
Erdafitinib	1	0%	5.0	0	na	na
Entrectinib	2	0%	1.5	2	0%	2.0
Fam-trastuzumab deruxtecan-nxki	2	0%	2.5	1	0%	1.0
Idecabtagene vicleucel	2	50%	4.0	1	0%	2.0



Regulatory bodies: US FDA, EMA, Health Canada; HTA bodies: NICE (National Center for Health Care Excellence), G-BA (Federal Joint Committee), HAS (Hauté Autorite de Santé), pCODR (pan-Canadian Oncology Drug Review), PBAC (Pharmaceutical Benefits Advisory Committee). Source: Adapted from Jaksa A et al, Value Health 2022; 25(12):1967-1976.
Abbreviations: Ph- ALL, Philadelphia chromosome-negative relapsed/refractory B-cell precursor acute lymphoblastic leukemia; MRD, treatment of minimal residual disease; ALL, positive B-cell precursor acute lymphoblastic leukemia; SOC, standard of care.

Concern #1: Selection bias

- Characteristics of trial patients differ from those of trial-eligible patients in the external data source due to the selection process itself.
- Applying all eligibility criteria will help mitigate this bias.

FDA 2019: Erdafitinib in FGFR2/3+ mUC

Single-arm BLC2001 Ph2 trial using Flatiron-derived ECA

- **Treated at academic medical centers vs community oncology clinics.**
- **Erdafitinib patients primarily European (70%); all control patients from US.**
- **More stringent inclusion/exclusion criteria for erdafitinib.**

Genesis Research Real-World Examples

- **Inability to apply all eligibility criteria in the real-world data source.**
- **Index date selection in the presence of multiple eligible time zeros.**
- **Different study entry processes.**
  - Time from diagnosis to treatment initiation.
  - Timing of assessments for entry.
- **Non-concurrent real-world cohorts.**
- **Geographic variability.**

FGFR2/3+, fibroblast growth factor receptor-positive (alterations 2/3); mUC, metastatic urothelial cancer. Source: FDA Center for Drug Evaluation and Research. Application Number 212018Orig1s000: Other Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212018Orig1s000OtherR.pdf

Concern #2: Confounding due to non-randomization

- Randomized controlled trials balance observed and unobserved confounders.
- In the real-world, treatment decisions are influenced by practitioners and observed patient characteristics.
- As a result of differences in treatment groups, the naive treatment effect is biased.

FDA 2018: Blinatumomab for MRD+ ALL
(ECA: historic SOC study)

- **Potential confounders were not adjusted for (e.g. year of diagnosis, relapsed vs persistent MRD).**
- **Unbalanced prognostic factors.**
- **35% of patients in the blinatumomab study were removed in the propensity score analysis.**
- **Different proportions of patients receiving HSCT.**
- **78% (blinatumomab) vs 44% (control) patients received HSCT as the historic control study (2000+) is not contemporaneous with the blinatumomab study (2010+).**

Genesis Research Real-World Examples

- **Missing or unmeasured prognostic variables.**
  COG, com meds, gene expressions.
- **Inconsistent study definitions.**
  Metastatic disease, disease classification, line of therapy.
- **Influence of temporality on SOC, diagnostic pathways.**
  SOC changes over time.
  Patients receiving SOC change.

MRD, treatment of minimal residual disease; ALL, positive B-cell precursor acute lymphoblastic leukemia; SOC, standard of care; HSCT, hematopoietic stem cell transplantation.
Source: FDA Center for Drug Evaluation and Research. Application Number 125557Orig1s013. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/125557Orig1s013.pdf

Concern #3: Inconsistent outcome definitions

- Introduces bias into the treatment effect estimate because of misspecification.
- In the design phase, need to assess the comparability of endpoints on timing, measurement, reliability, validity.
- Real-world endpoints will (in most cases) not be fully aligned with trial.

FDA 2019: Entrectinib in ROS1-positive advanced NSCLC (ECA: crizotinib)

- **TTD is complicated by treatment beyond disease progression.**
- **PFS is limited by missing or infrequent radiographic imaging within electronic medical record data; Assessment of potential bias should be evaluated with ongoing sensitivity analysis.**

Genesis Research Real-World Examples

- **Incomplete or misspecified endpoint information.**
  Survival, complete response.
- **Undefined real-world criteria.**
  Variability, subjectivity.
  Trials: Lugano, RECIST, CTCAE.
- **Unsystematic timing and frequency of endpoint assessment.**
  Schedule of assessments in trials.

NSCLC, non small cell lung cancer; TTD, time to treatment discontinue; mUC, PFS, progression-free-survival; OS, overall survival; IPTW, inverse probability weighting.
Source: FDA Center for Drug Evaluation and Research. Application Number 212725Orig1s000: 212726Orig1s000: Other Review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000Approv.pdf

Engage regulatory/HTA bodies early in design phase

FDA

- ✓ Type B or C meeting.
- ✓ Collaborate w/ FDA on design (FDA review of protocol early in design phase).

EMA

- ✓ Early discussions involving relevant Rapporteurs or Lead Member States and HTA bodies.
- ✓ Non-binding Scientific Advice (available at any stage) or Protocol Assistance (orphan medications).

HTA (EU)

- ✓ Joint Scientific Consultations recommended after feasibility assessment/proof of concept completion but prior to study kick-off.
- ✓ NICE Scientific Advice, G-BA's Early Advice, HAS Early Dialogues.

U.S. FDA. Center for Drugs Evaluation Research. February 2023. Considerations for the Design and Conduct of Externally Contrdled Trials for Drug and Biological Products: Draft Guidance for Industry. Rockville, MD.

European Medicines Agency. Scientific Advice and Protocol Assistance. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-adviceprotocolassistance#:~:text=EMA%20gives%20scientific%20advice%20by,development%20of%20a%20particu lar%20medicine.&text=Scientific%20advice%20from%20EMA%20is,applications%20for%20the%20medicine%20concerned

European Medicines Agency. Guideline on registry-based studies. <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based studiesen-0.pdf> (2021).

Curtis LH et all Regulatory and HTA Considerations for Development of Real-World Data Derived External Controls. Clinical Pharmacology and Therapeutics (in press, https://doi.org/10.1002/cpt.2913)

Fit-for-purpose external control arms: key points

1

External control arm studies require **early planning and thoughtful design** that mitigates potential sources of bias.

2

Regulatory & HTA agencies' common **critiques of ECA methodological challenges** include selection bias, unmeasured confounding, and non-comparability of study endpoints between the trial and external control patient populations.

3

Early and collaborative engagement of regulatory and HTA bodies is recommended to align on study objectives and methodological approach.

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A **better way** to optimize insights and evidence

Questions? If you would like to discuss this presentation further or arrange a meeting, please visit us at **BOOTH 839** or contact **solutions@genesisrg.com**