Cytel

Ahead of the Curve: Navigating Early Planning Strategies for External Control Arms in HTA and Regulatory Submissions

ISPOR HEOR Theatre

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Today’s presenters

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What's trending in the use of External Control Arms

Regulatory & HTA

- Successful submissions using ECAs
- Formal guidance on ECA standards

Manufacturers

- Driven to lower clinical development costs
- ECA use outside of regulatory/HTA purpose

Data innovation

- Better quality RWD
- Common data models and harmonization

Analytics

- Complex analytical approaches
- Hybrid designs

Abbreviations: ECA, external control arm; HTA, health technology assessment; RWD, real-world data

Best practices from regulatory and HTA guidance

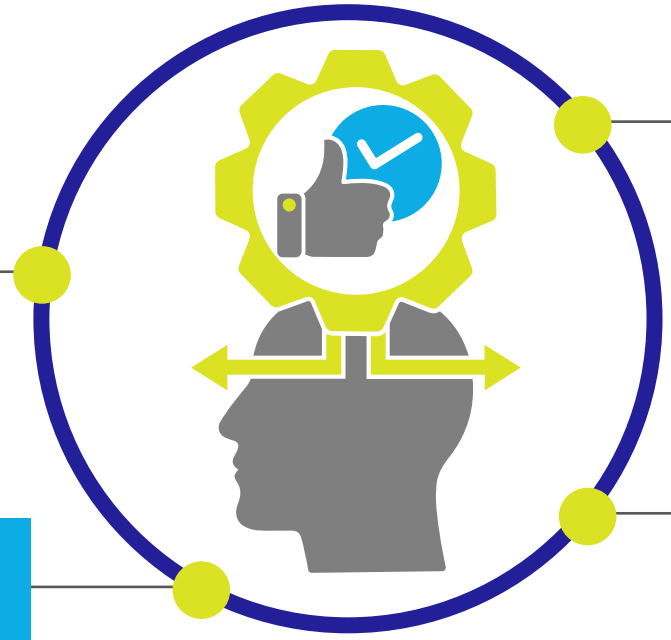
Several regulatory and HTA agencies have issued guidance on ECAs with common principles

Data source selection & justification

- Systematic and transparent **feasibility assessment**
- Data provenance and quality
- Coverage of key variables (inclusion criteria, consistent endpoints, confounders)
- Missingness

Methods to address bias

- Extensive sensitivity analyses
- Quantitative bias analysis



Study design

- Target trial emulation
- Pre-specification
- **Comparability** between trial and external groups

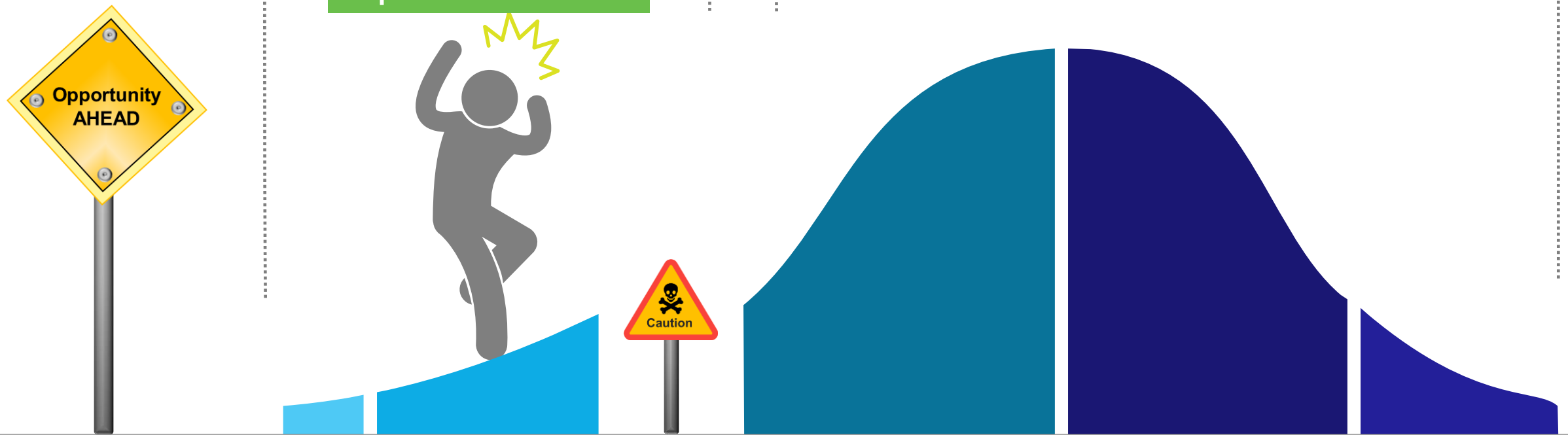
Early engagement

- Early scientific advice programs
- Justify rationale for ECA
- Collaborate with agencies on study design

Abbreviations: ECA, external control arm; HTA, health technology assessment

Sponsors need to plan early, and align cross-functionally for reliable and impactful ECAs

ECA guidance is helpful, but key questions remain:

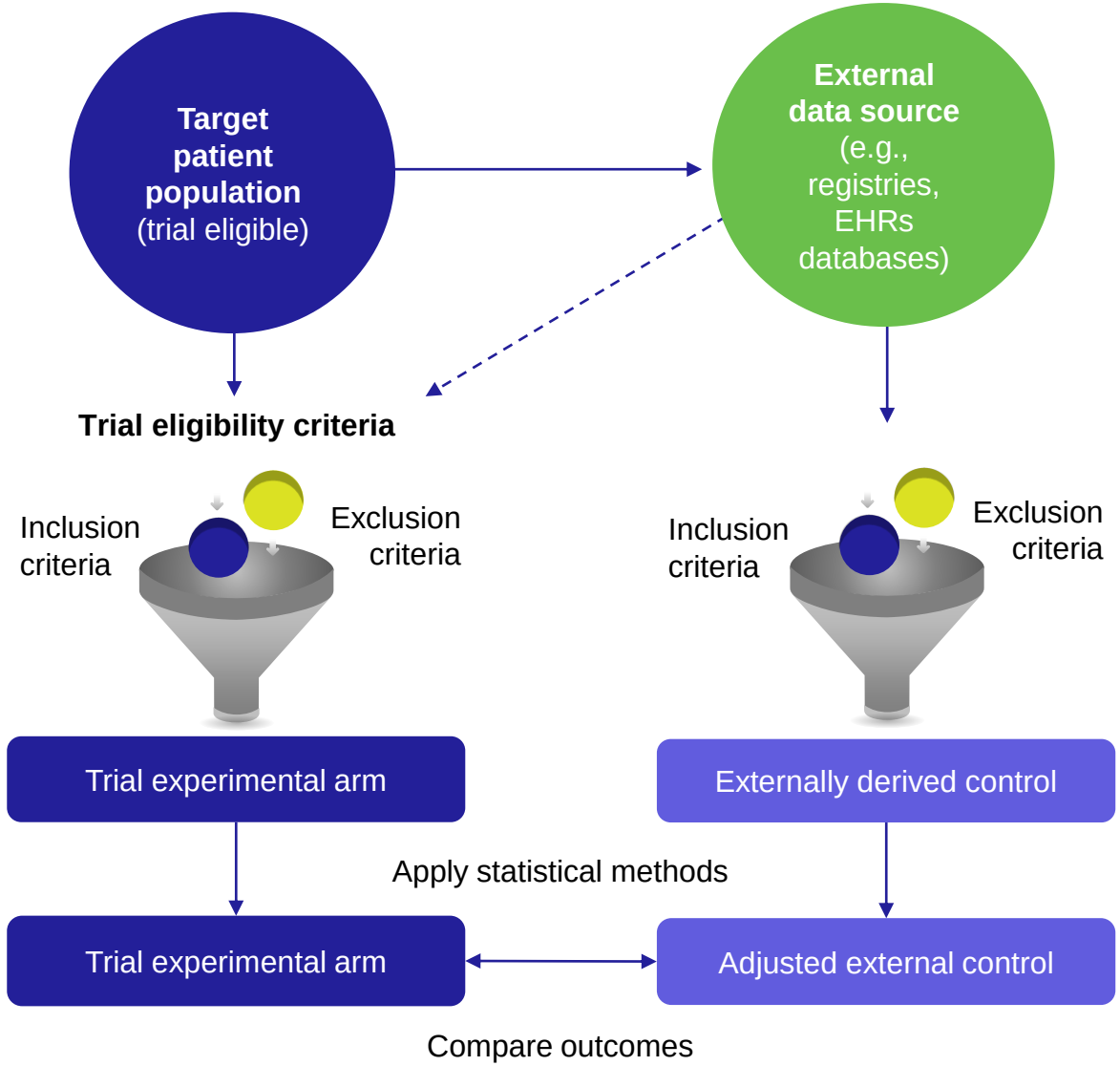


When is the most optimal timing in the development process to plan for an ECA?

When and how should a company best prepare for early interactions to address differing regulatory and HTA perspectives?

Abbreviations: ECA, external control arm; HTA, health technology assessment

ECAs



Use of ECAs along the product lifecycle

Early-phase 1–2 trials

- Natural history studies
- SAT direct comparisons with RWD-derived ECA

Late-phase 3 trials

- Hybrid trials (control groups built with mix of randomized controls from RCT and ECA from RWD or historical trial data)

Regulatory/HTA submissions

- ITCs

Post-marketing

- Post-marketing comparative safety and effectiveness studies (in absence of unexposed group)

Abbreviations: ECA, external control arm; EHR, electronic health record; HTA, health technology assessment; ITC, indirect treatment comparison; RWD, real-world data; RCT, randomized controlled trial; SAT, single-arm trial

What have we learned on the acceptability of ECAs in regulatory and HTA?

Case Study of Single Arm Submission with ECA

- Tafasitamab (Monjuvi) with lenalidomide in relapsed or refractory diffuse large B-cell lymphoma
- L-MIND –phase II single-arm trial + matched control from RE-MIND observational cohort study using EHR data

- ❑ **FDA (2019)**: The agency provided early advice on the design of the observational study- main critiques:
  - cohort not representative of target population, small sample size, interpretability of study endpoints and outcome misclassification, relevance of confounders.
- ❑ **Sponsor strategy:** Provided extensive sensitivity analyses to address FDA's feedback on the design and data limitations
- ❑ **Final decision**: **Approval**

(although the FDA acknowledged several limitations with the observational study)

- ❑ **NICE (2022)**: The committee noted uncertainty in the results of the indirect evidence against comparators, including imbalance of baseline characteristics. Methods were found complex and unclear, with high risk of potential bias.

- ❑ **Final decision**: **Not recommended**

Despite converging requirements in formal guidance, regulatory vs. HTA perspectives differ

Regulatory

- ✓ Focus on assessing benefit-risk balance
- ✓ May not include comparisons with other active treatment (e.g., single-arm, or placebo-controlled trials)

Important to gain unbiased clinically significant **treatment effect**

HTA

- ✓ Focus on evaluating effects against relevant comparators
- ✓ May differ from regulators about which comparators are relevant (may differ between countries)

Important to gain unbiased **treatment effect size** and consider how this extends to estimate of cost-effectiveness

Abbreviation: HTA, health technology assessment

HTA criteria also very between countries.. the EU JCA further complicates evidence generation activities

- JCA report = assessment report of clinical effectiveness (not a recommendation)
- <u>Reimbursement and pricing decisions made at the national level</u>

Challenges

- Lack of standardized criteria among HTA agencies in each country
- Different acceptance thresholds (e.g., historically lower acceptance of RWE in Germany)
- Different definitions of target populations
- Different definitions of relevant current standard of care/comparators, etc.

Multiple considerations and complexities for RWE generation → **operational and financial pressure**

Abbreviations: EU, European Union; HTA, health technology assessment; JCA, Joint Clinical Assessment; RWE, real-world evidence

Is early advice the answer?

Early advice is strongly encouraged but success is not guaranteed

Case Study of Single Arm Submission with ECA[1]

- Idelalisib- previously indicated for CLL, sponsor submitted application for indication expansion to include FL.
- DELTA -phase II single-arm study and RWD from the UK HMRN, a population-based registry

Sponsor sought early advice

NICE in final appraisal expressed concerns about the comparability of RWD to trial patients, limited sample sizes, missing data, confounding bias, no sensitivity analyses using other matching methods

Final decision: **Not recommended**

*"Sponsors planning to use a non-interventional study to support a marketing application **should engage with FDA early in the drug development process** using an appropriate regulatory pathway (e.g., requesting a Type C meeting through an existing IND for the product)".* (FDA RWE Guidance, 2023)

*"We encourage companies planning to use real-world data in their submissions to **engage early with NICE Scientific Advice** on how to make best use of real-world data as part of their evidence-generation plans"* (NICE, RWE Framework, 2022)

1. Adapted from Curtis LH at al,Regulatory and HTA Considerations for Development of Real-World Data Derived External Controls. Clin Pharmacol Ther. 2023 Aug;114(2):303-315. doi: 10.1002/cpt.2913. Epub 2023 Jun 9. PMID: 37078264.

Abbreviations: CLL, Chronic lymphocytic leukemia; ECA, external control arms; FL, follicular lymphoma; RWD, real-world data

Optimal timing for ECA planning and early external engagement

❑ Internally

- Alongside the clinical development program/ clinical trial design (ideally)
    - Opportunities to gain experience with RWD, make investment decisions for data improvements (e.g., data collection and infrastructure)
    - Opportunities to allow for real-world endpoints in clinical trial design

❑ Externally (regulators and payers)

- Timing of the engagements is contextual but should be early enough for adjustments to RWD strategy and study design (pre-protocol/SAP finalization)

- e.g., Adjustments to RWD strategy such as...
    - data augmentation
    - data validation
    - inclusion of additional sources
- Alternative study designs, methods to address data limitations

Early **cross-functional alignment** is key for aligning on study objectives and efficient evidence planning

What should the sponsors cover in early engagements?

Rationale for an ECA

- Multi-pronged approaches combining engagement with stakeholders, patient groups, literature review (LR), assessing sparsity of available data are recommended.

Data source selection, access, and justification

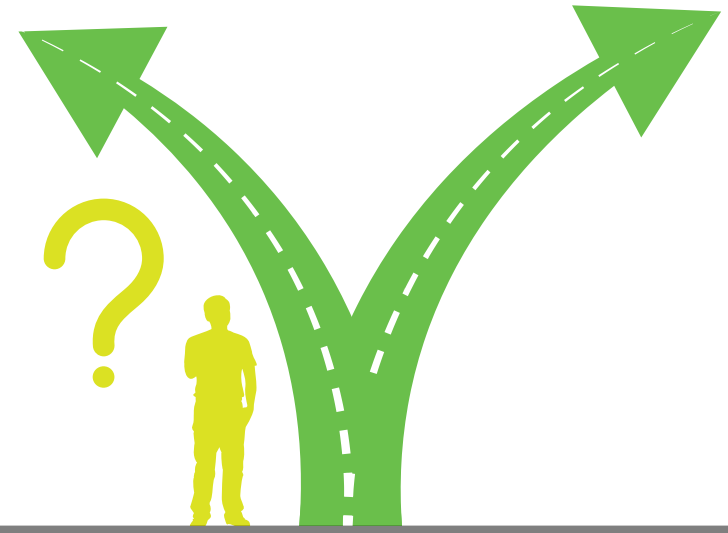
- This requires a systematic/transparent data selection process, LR, access and feasibility

Early ECA study design

- To get ahead of potential risks and fully get the most from early engagements, the design should address potential bias concerns, requiring feasibility assessments.

Feasibility assessment

- This will inform data source selection, justification, and study design.
- It will also answer key questions regarding sample sizes, sources of bias, missing data, etc.



Pathways for early advice:

- **FDA**: Type C meeting
- **EMA**: Early discussions
- **HTA**: NICE Early Scientific Advice, G-BA etc
- Joint scientific consultations

Sample timeline (months)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Rationale for an ECA																
Data selection, access and justification																
Early ECA study design																
Feasibility assessment																

Abbreviations: ECA, external control arm; EMA, European Medicines Agency; FDA, Food and Drug Administration; G-BA, Germany's Joint Federal Committee; HTA, health technology assessment; LR, literature review; NICE, National Institute for Health and Care Excellence

The most common problems and solutions

Case #1 Small sample size – comparative effectiveness in NSCLC

Sample size

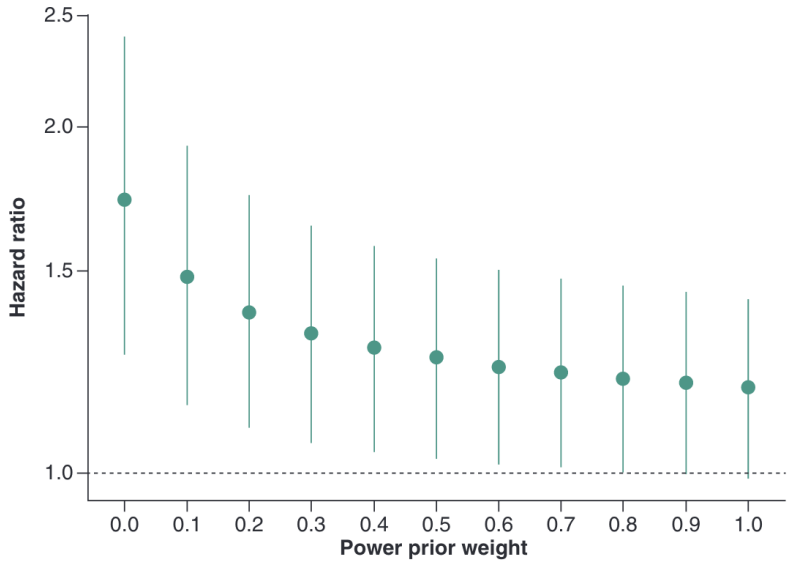
- **Objective**: Compare OS for cetuximab + carboplatin + paclitaxel vs. carboplatin + paclitaxel for supporting evidence as part of HTA and market access activities
- **Challenge**: Small sample sizes limit study power, and precision of effect estimates
- **Solution**: Cytel performed *cardinality matching* and *Bayesian borrowing* to use multiple external data sources to increase power and precision.
- **Results**: Showed Bayesian borrowing increases the precision of study estimates

OPEN ACCESS | Research Article | 4 April 2024

Augmenting external control arms using Bayesian borrowing: a case study in first-line non-small cell lung cancer

Authors: Alessandria Struebing, Chelsea McKibbon, Haoyao Ruan, Emma Mackay, Natalie Dennis, Russanthy Velummailum, Philip He, Yoko Tanaka, Yan Xiong, Aaron Springford, and Mats Rosenlund | AUTHOR INFO & AFFILIATIONS

Publication: Journal of Comparative Effectiveness Research • Volume 13, Number 5 • https://doi.org/10.57264/cer-2023-0175



Use of Bayesian borrowing requires increased planning time, and scale of sensitivity analyses.

Abbreviation: HTA, health technology assessment; NSCLC, non-small cell lung cancer; OS, overall survival

The most common problems and solutions

Case #2 Bias from missing data and unmeasured confounding

Bias

- **Objective**: Compare OS of alectinib vs ceritinib in overall survival in patients with ALK-positive, crizotinib-refractory NSCLC for supporting evidence as part of health technology assessments (HTA) activities
- **Challenge**: To assess the sensitivity of study estimates to unmeasured confounding and missing data assumptions
- **Solution**: Cytel performed *quantitative bias analysis (QBA)* to estimate the impact of residual confounding by a hypothetical confounder and robustness to deviations from various missingness assumptions
- **Results**: Showed that study findings were robust under all plausible assumptions of missingness and unmeasured confounding

Original Investigation | Oncology

October 7, 2021

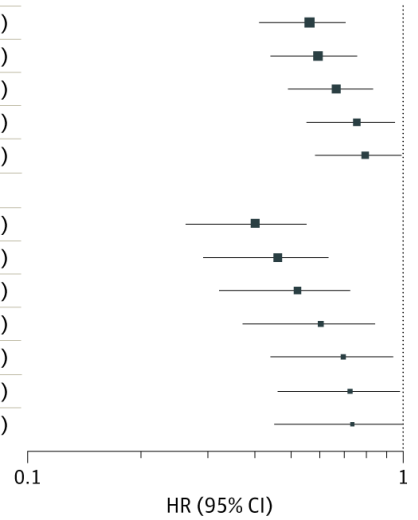
Assessment of Alectinib vs Ceritinib in *ALK*-Positive Non-Small Cell Lung Cancer in Phase 2 Trials and in Real-world Data

Samantha Wilkinson, PhD[1]; Alind Gupta, PhD[2]; Nicolas Scheuer, PhD[3]; Eric Mackay, MA, MSc[2]; Paul Arora, PhD[2]; Kristian Thorlund, PhD[2]; Radek Wasiak, PhD[2]; Joshua Ray, MSc[4]; Sreeram Ramagopalan, PhD[4]; Vivek Subbiah, MD[5,6]

Study cited by NICE

Figure. Tipping Point Analysis for Missing Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

Trial-RWD	HR (95% CI)
δ=1	0.56 (0.41-0.70)
0	0.59 (0.44-0.75)
-1	0.66 (0.49-0.83)
-2	0.75 (0.55-0.95)
-3	0.79 (0.58-0.99)
RWD-RWD	
1	0.40 (0.26-0.55)
0	0.46 (0.29-0.63)
-1	0.52 (0.32-0.72)
-2	0.60 (0.37-0.84)
-3	0.69 (0.44-0.94)
-4	0.72 (0.46-0.98)
-5	0.73 (0.45-1.00)



In accordance to NICE and FDA guidance, all QBA should be pre-specified in study protocols.

Abbreviation: HTA, health technology assessment; NSCLC, non-small cell lung cancer; QBA, quantitative bias analysis

The most common problems and solutions

Sample size

- Often suspected beforehand, fully confirmed in a feasibility assessment
- When not addressed early enough, can greatly risk an uninformative analysis and extend timelines

- Statistical adjustment methods
- Leverage multiple data sources simultaneously via **Bayesian borrowing**
  - Potential for high effectiveness, but substantially increases feasibility assessment, design, and analysis time

Bias

- Caused by data defects: missing data, unmeasured confounders, variable precision, mis-measured variables, etc.
- Comparability between RWD and trial cohorts

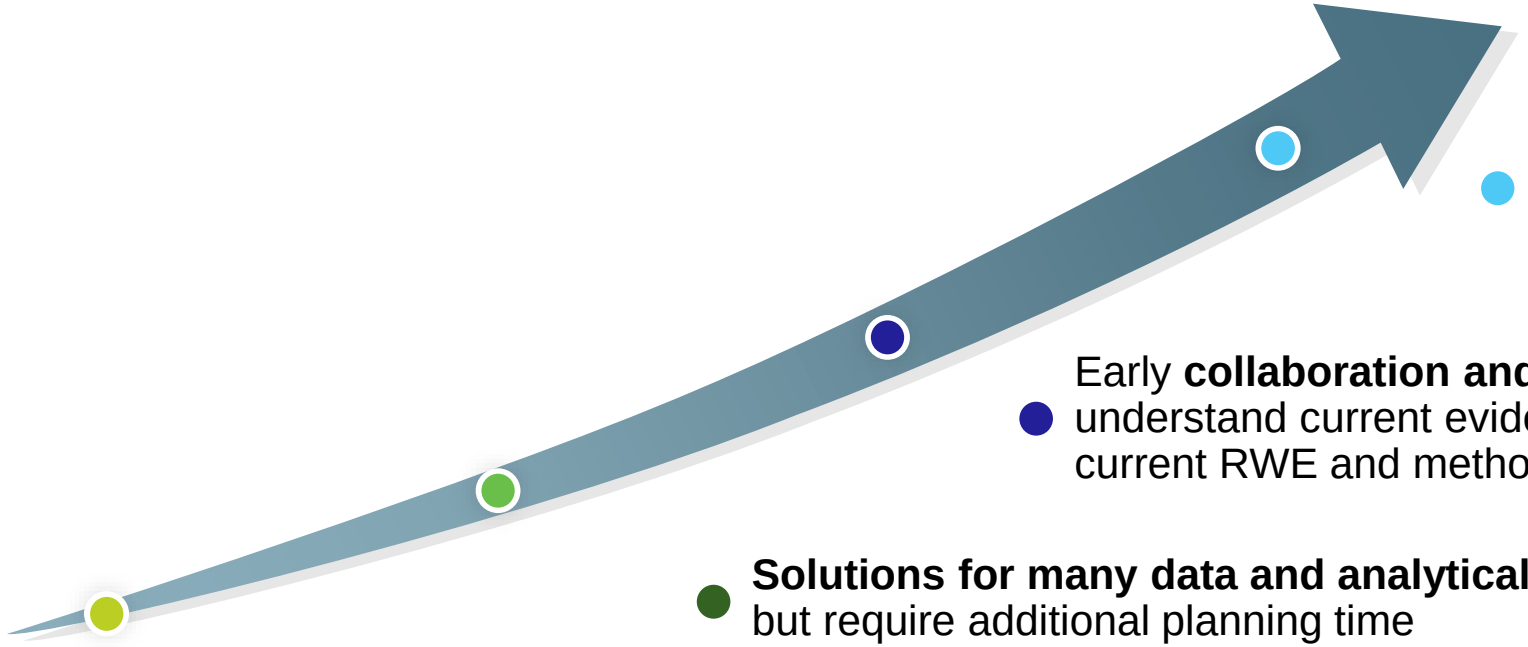
- **Quantitative bias analysis** can greatly improve study robustness, but requires increased design and analysis time

Recommended by FDA, NICE, CADTH, HAS etc.

Solutions should be covered in early engagements, with *increased planning* and *execution time* in mind.

Abbreviation: RWD, real-world data

Early strategies for ECAs: takeaways



- Early **cross-functional alignment** is key for aligning on study objectives and efficient evidence planning
- Early **collaboration and discussion with decision makers** helps understand current evidence gaps and trade-offs in uncertainties with current RWE and methods
- **Solutions for many data and analytical challenges are available** but require additional planning time
- **Planning for ECAs early** in the development process allows better study design decisions
- **ECAs are not preferred but can be acceptable** under certain conditions if rationale is clear and ECA is well designed

Moderated Q&A

Thank you.

Do you have questions?
Please visit us at **Booth #1018** or contact our speakers

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Cytel Publications

Struebing A, McKibbon C, Ruan H, Mackay E, Dennis N, Velummailum R, He P, Tanaka Y, Xiong Y, Springford A, Rosenlund M. Augmenting external control arms using Bayesian borrowing: a case study in first-line non-small cell lung cancer. J Comp Eff Res. 2024 Apr 4:e230175. doi: 10.57264/cer-2023-0175. Epub ahead of print. PMID: 38573331.

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Jason Simeone, PhD
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Jason has over 15 years of experience in pharmacoepidemiology and database analytics, and his global research has focused on medication safety, effectiveness, burden of illness, and treatment patterns in a wide range of therapeutic areas, with experience conducting retrospective PASS studies and multi-country studies. He is particularly interested in the application of RWE for regulatory decision-making and has served as a member of several Duke-Margolis Real-World Evidence Collaborative working groups. He has an MS and PhD from the University of Rhode Island in pharmacoepidemiology and pharmacoeconomics.

Evie Merinopoulou, MSc
Senior Director, RWE
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Evie Merinopoulou is a Health Economist and Real-World Data Scientist working on applications of Real-World Evidence in support of regulatory and HTA decision making. Ms Merinopoulou has worked in the healthcare consulting industry for 12 years. She currently serves as a Senior Director, Real-World Evidence at Cytel, based in London, UK. She leads the design and execution of observational research projects using global real-world data. Ms Merinopoulou particularly focuses on studies involving real-world external comparator arms, quantitative bias analysis, head-to-head comparisons using target trial emulation, and transportability analysis.

Grace Hsu, MSc
Director, RWE
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Grace is Director of Real-World Evidence at Cytel with 9 years of experience in consulting and guiding project strategies. She holds a Master's degree in Statistics, providing statistical consulting and strategy development for data curation, and the application of advanced analytics to clinical and RWD. Examples of her peer-reviewed publications include work on COVID-19, synthetic/external control arm comparative effectiveness analysis, quantitative bias analysis, Bayesian borrowing and other methods of indirect comparison for both pharmaceutical research and HTA/regulatory submissions.