

BACKGROUND & OBJECTIVE

Why ECAs?

- Generate comparative evidence when randomization is infeasible, unethical, or insufficient.
- Use historical trials, registries, electronic health records, claims, or observational cohorts as external comparators.
- Support single-arm evidence or augment a smaller concurrent control in a hybrid design.

Objective

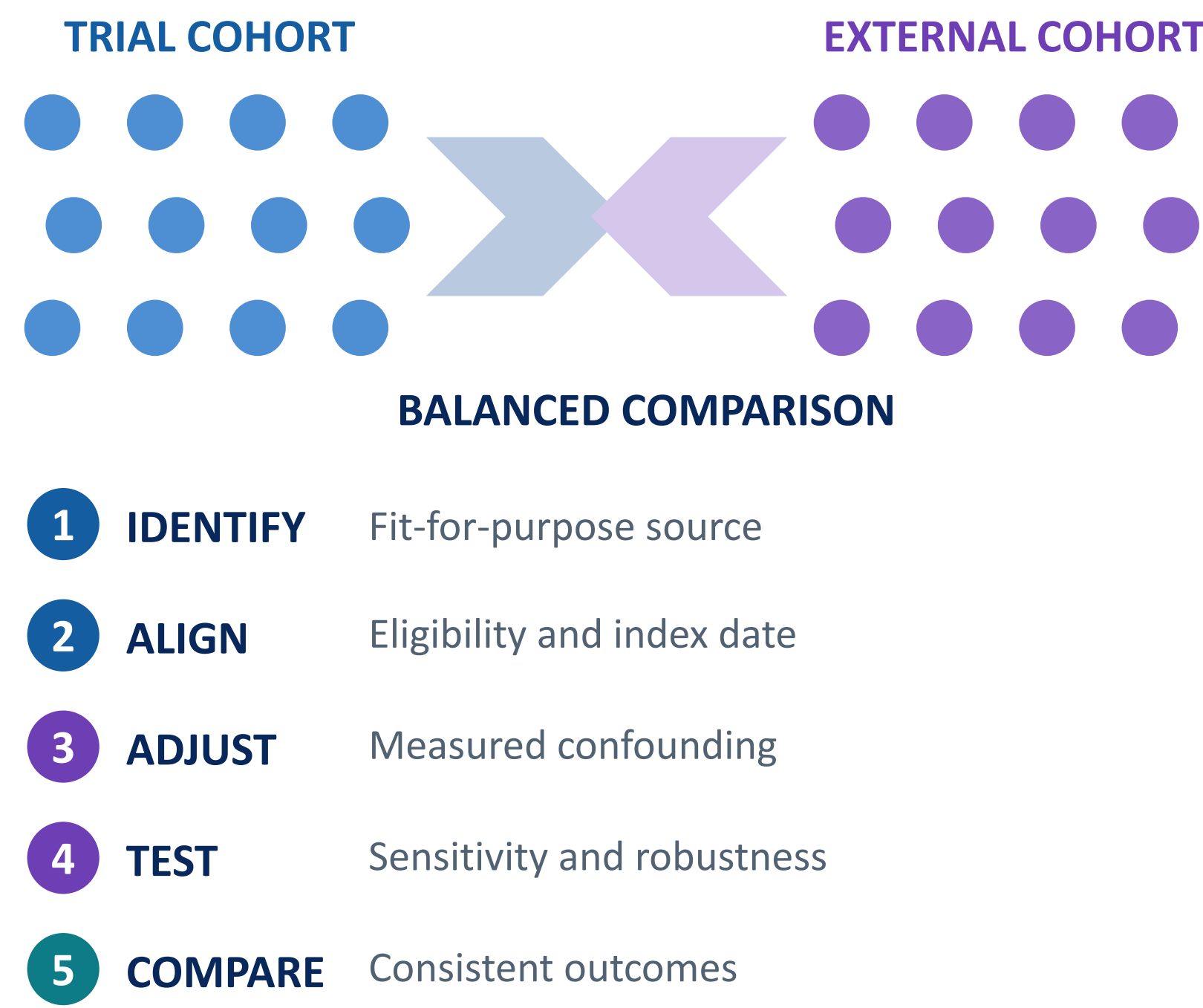
Characterize regulatory and HTA expectations, summarize patterns of acceptance and rejection, and assess targeted ECA-supported and hybrid applications in asthma.

METHODS

Structured methodological synthesis

- Reviewed guidance and frameworks from FDA, EMA, NICE, CADTH, PMDA, MHRA, and EUnetHTA.
- Assessed data-source selection, eligibility alignment, endpoint consistency, baseline comparability, and confounding control.
- Examined propensity score matching, inverse probability weighting, covariate adjustment, sensitivity analyses, and Bayesian dynamic borrowing.
- Considered ECAs across early development, hybrid trials, HTA submissions, and extension or post-marketing studies.

ECA DESIGN LOGIC



ACCEPTANCE CRITERIA

DATA SOURCE	Clearly identified, characterized, and supported by validation or quality standards.
COMPARABILITY	Eligibility aligned; key baseline characteristics documented; overlap demonstrated.
ENDPOINTS	Same or validated endpoints with comparable definitions and assessment timing.
ANALYTICS	Validated adjustment methods, pre-specified plan, confidence intervals, and sensitivity analyses.
CLINICAL RATIONALE	Biological and disease-context justification for using an external comparator rather than an RCT.

CROSS-AGENCY CONSENSUS

Shared expectations

- Early engagement is recommended.
- Design justification, protocol, and analysis plan should be pre-specified.
- Suitability is assessed case by case based on fitness for purpose and comparability.
- Transparent data access, analysis, and reporting are expected.

Relative preference in multi-treatment settings

1

Head-to-head randomized evidence

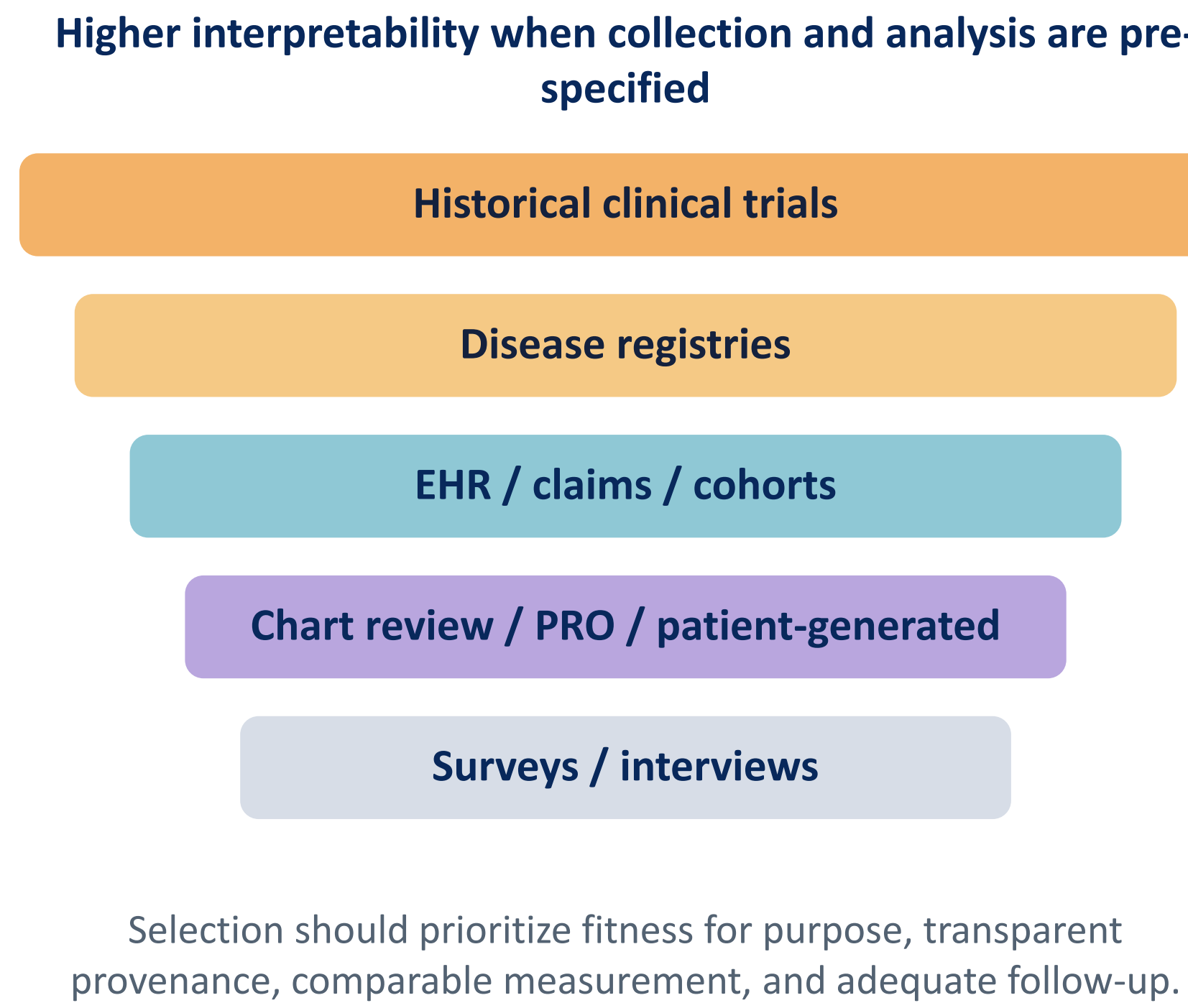
2

Anchored indirect comparison / NMA

3

External control arm when alternatives are infeasible

DATA-SOURCE LADDER



WHERE ECAs ADD VALUE

ETHICS	Avoid prolonged placebo when inappropriate.
FEASIBILITY	Address small populations and recruitment constraints.
CONTEXT	Reflect routine-care populations and standard practice.
EFFICIENCY	Augment a small randomized control in hybrid designs.
LONG-TERM	Contextualize extension or post-marketing outcomes.

SYNTHESIZED RESULTS

Acceptance pattern

- Accepted when supported by clear clinical rationale, well-defined external cohorts, baseline comparability, and pre-specified analytical approaches.
- Acceptance was most frequent in oncology and rare diseases, where feasibility is limited and endpoints are well validated.
- Rejections were linked to population heterogeneity, analytical limitations, and incomplete outcome capture.
- HTA recommendations were more favorable when ECAs were anchored to prior trials or robust real-world data.

ECAs complement rather than replace randomized evidence.

TARGETED APPLICATIONS IN ASTHMA

1	HYBRID DESIGNS	Augment a smaller concurrent control when heterogeneity or recruitment burden is high.
2	RARE PHENOTYPES	Contextualize evidence where conventional randomization is impractical.
3	EXTENSION STUDIES	Provide long-term comparative context after randomized follow-up ends.
4	POST-APPROVAL RWE	Assess effectiveness, durability, and subgroup outcomes in routine care.

PRACTICAL DECISION CHECK

- ✓ Is randomization infeasible or inappropriate?
- ✓ Is the external source fit for purpose?
- ✓ Can the trial and external populations be aligned?
- ✓ Are endpoint definitions and timing consistent?
- ✓ Can residual confounding be characterized?
- ✓ Is the analysis fully pre-specified and reproducible?

CONCLUSIONS

- ECAs are a complementary evidence approach when methodological rigor and clinical plausibility are demonstrated.
- Transparent cohort construction, comparable outcomes, and robust sensitivity analyses are central to acceptance.
- In asthma, targeted use in hybrid, rare-phenotype, extension, and post-approval settings may address long-term evidence gaps.

ECAs are most defensible when the clinical rationale, external cohort, endpoint timing, baseline comparability, and analyses are prospectively specified and transparent.

ABBREVIATIONS

CADTH, Canadian Agency for Drugs and Technologies in Health; ECA, external control arm; EHR, electronic health record; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment; IPTW, inverse probability of treatment weighting; MHRA, Medicines and Healthcare products Regulatory Agency; NMA, network meta-analysis; NICE, National Institute for Health and Care Excellence; PMDA, Pharmaceuticals and Medical Devices Agency; PSM, propensity score matching; RCT, randomized controlled trial; RWD, real-world data.

ISPOR ASIA PACIFIC SUMMIT 2026

Poster HTA24 | Session 2

Monday, 7 September 2026
12:15–16:15