Application of Meta-Analysis Approach to Develop an External Control Arm in Oncology and Rare Diseases: Insights From Real-World Evidence

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Introduction

- The availability of diverse real-world data (RWD) or real-world evidence (RWE) emphasizes the use of external control arm (ECA) comparator when randomization is deemed infeasible/unethical in randomized controlled trials (RCTs), or when a single-arm trial design is elected [1].
- The growing interest in real-world external comparators (RWEC) in oncology and rare diseases accentuates the need for extended application of meta-analysis (MA) with advanced epidemiological methods for expanded use of RWD/RWE.

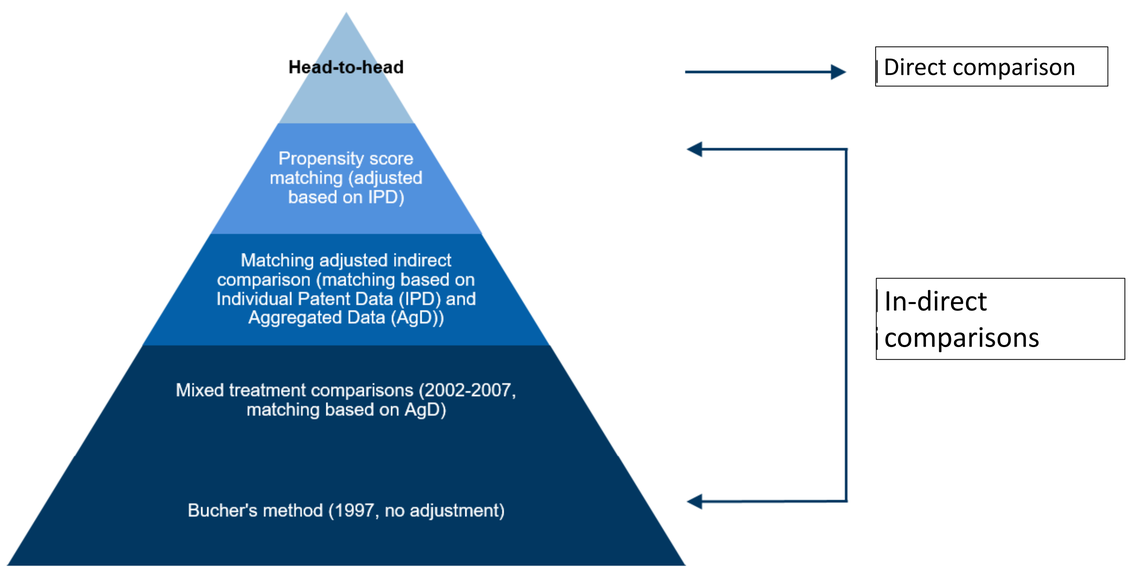
Objective

- To demonstrate the utilization of meta-analysis approach to develop external control arm as comparator in Oncology and rare diseases.

Methods

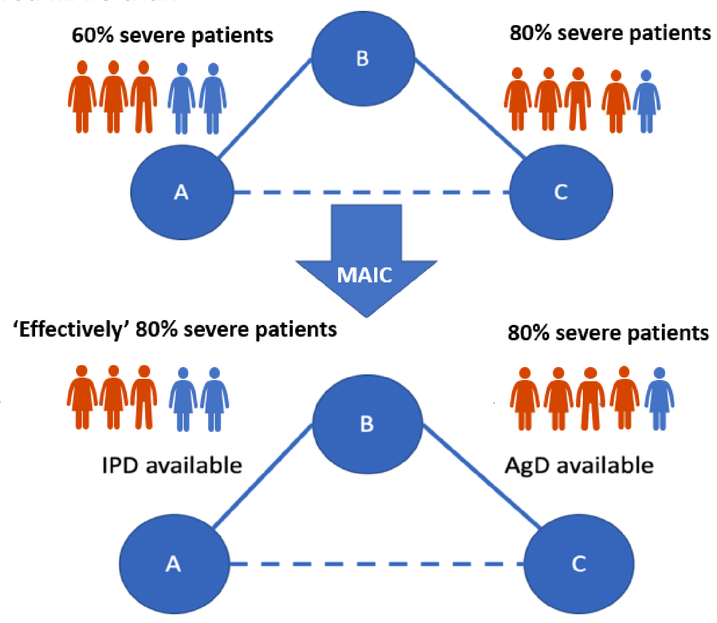
- A RWEC built from RWD includes patient-level characteristics with appropriate matching, allowing for direct and indirect matching between patients in the external and index cohorts.
- For direct comparisons, the data from comparator are combined in the same research database as index-cohort patient data (Figure-1). For indirect comparisons, Individual patient date (IPD) and aggregated data (AgD) from the literature will be extracted based on meta-analysis framework and matched with controls using advanced epidemiological methods.

Figure-1: Pyramid of direct and indirect comparisons:



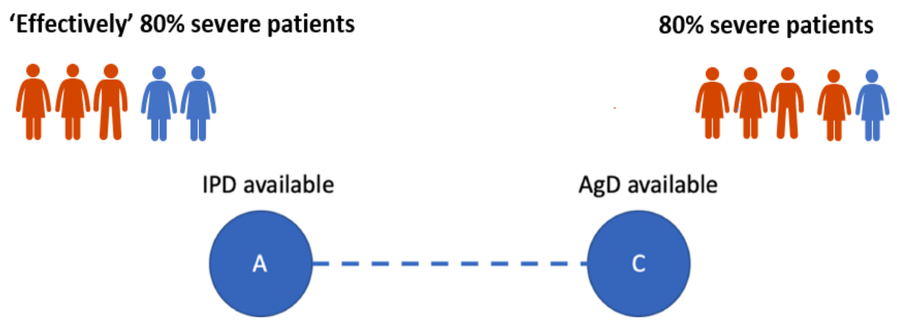
- Among indirect comparisons, matching-adjusted Indirect comparisons (MAIC) is commonly used technique where it can be used for anchored trial[7] and unanchored trials[8]. Anchored trials are performed with inclusion of IPD and AgD whereas, unanchored is commonly used when there are two single armed trials..
- Using individual patient data (IPD) from one trial and aggregate data (AgD) from another, MAIC adjusts for potential bias while a simple indirect comparison does not account for potential discrepancies in the A vs. B and B vs. C trials (Figure-2).
- Pre-requisites of conducting an anchored MAIC are:
  - A connected network of clinical trials that includes the interventions of interest exists
  - IPD is available for at least one trial and AgD from another
  - The IPD and AgD both contain information on the main covariates of interest that require adjustment for
- A combination of MAIC with Network meta-analysis (NMA) are commonly used in developing ECAs [2]

Figure-2: Anchored MAIC trial:



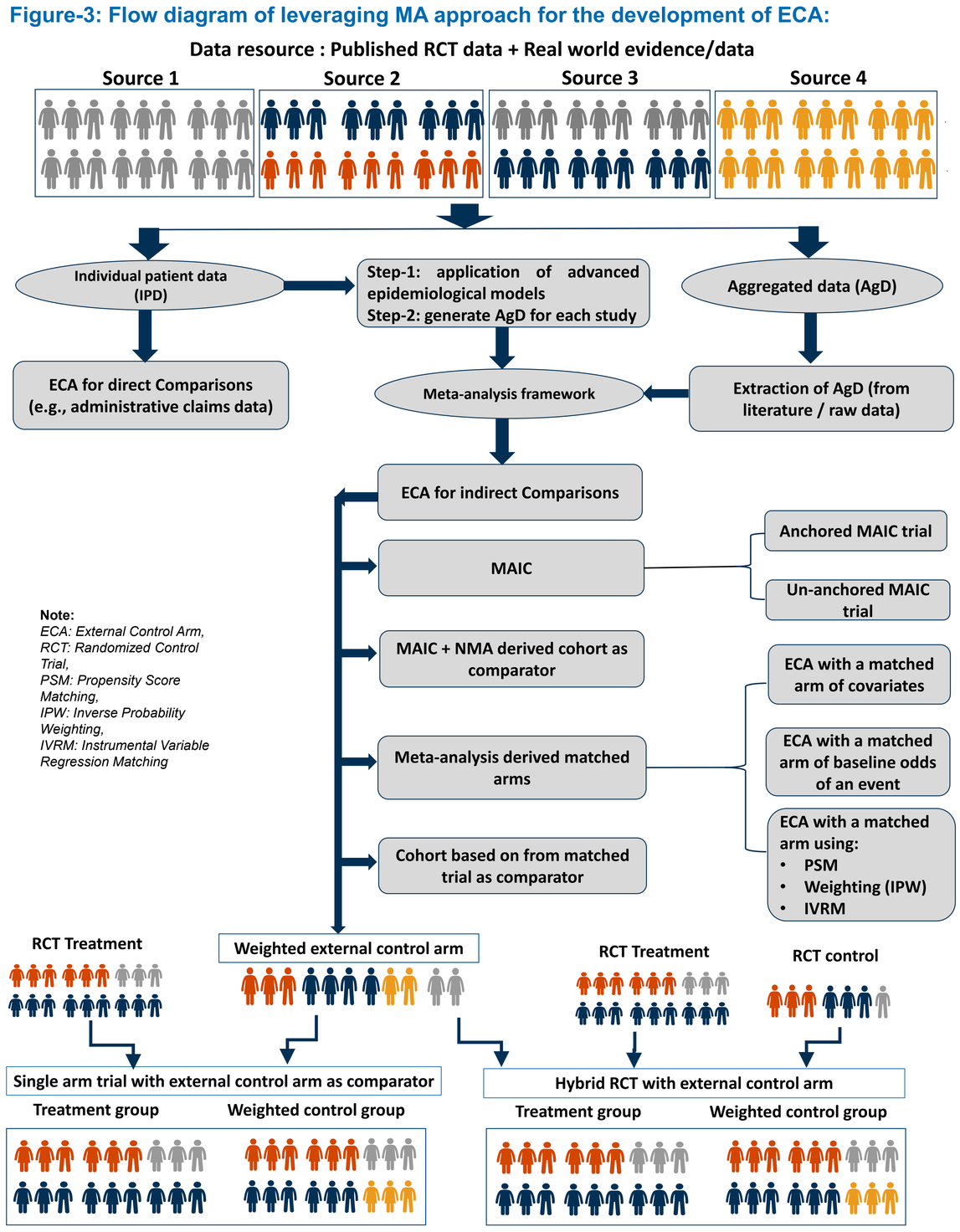
- An unanchored MAIC would be required if trials vs B did not exist, and there are only two single-arm trials that investigated the effects of A and C independently.

Figure-2.1: Un-anchored MAIC trial



- In single-arm studies, aggregate level covariates are incorporated using a matched-arm of covariates in the dataset as a comparator or using the baseline odds of an event in a chosen matched trial from MA

Figure-3: Flow diagram of leveraging MA approach for the development of ECA:



Results:

- MAIC approach compared first-in-class immunotherapy agents and orphan medical products to existing therapies in rare diseases like relapsed/refractory diffuse large B-cell lymphoma, and mantle cell carcinoma (n=2) [3].
- Similarly, MAIC and NMA have been used to generate ECA for single-arm studies comparing immunotherapy agents and combinations with existing lines of treatment for advanced cancers (e.g., hepatocellular carcinoma and melanoma; n=2) [2].
- Recent regulatory approvals in immunotherapy by the USFDA and EMA, besides health technology assessors' guidelines for use of MAIC, point to an increase in the use of better fit-for-purpose ECA [1,5].

Conclusions

The underutilized advanced epidemiologic methods combined with MA approach can be used to

- generate relevant evidence,
- gain regulatory poise, and
- accelerate access to newer therapies with ECA developed from RWD/RWE/existing RCTs/trials.

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Disclosures

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