Data & Statistical Sciences

Population-adjusted Indirect Comparisons in Rare Diseases: Methods, Challenges and Considerations

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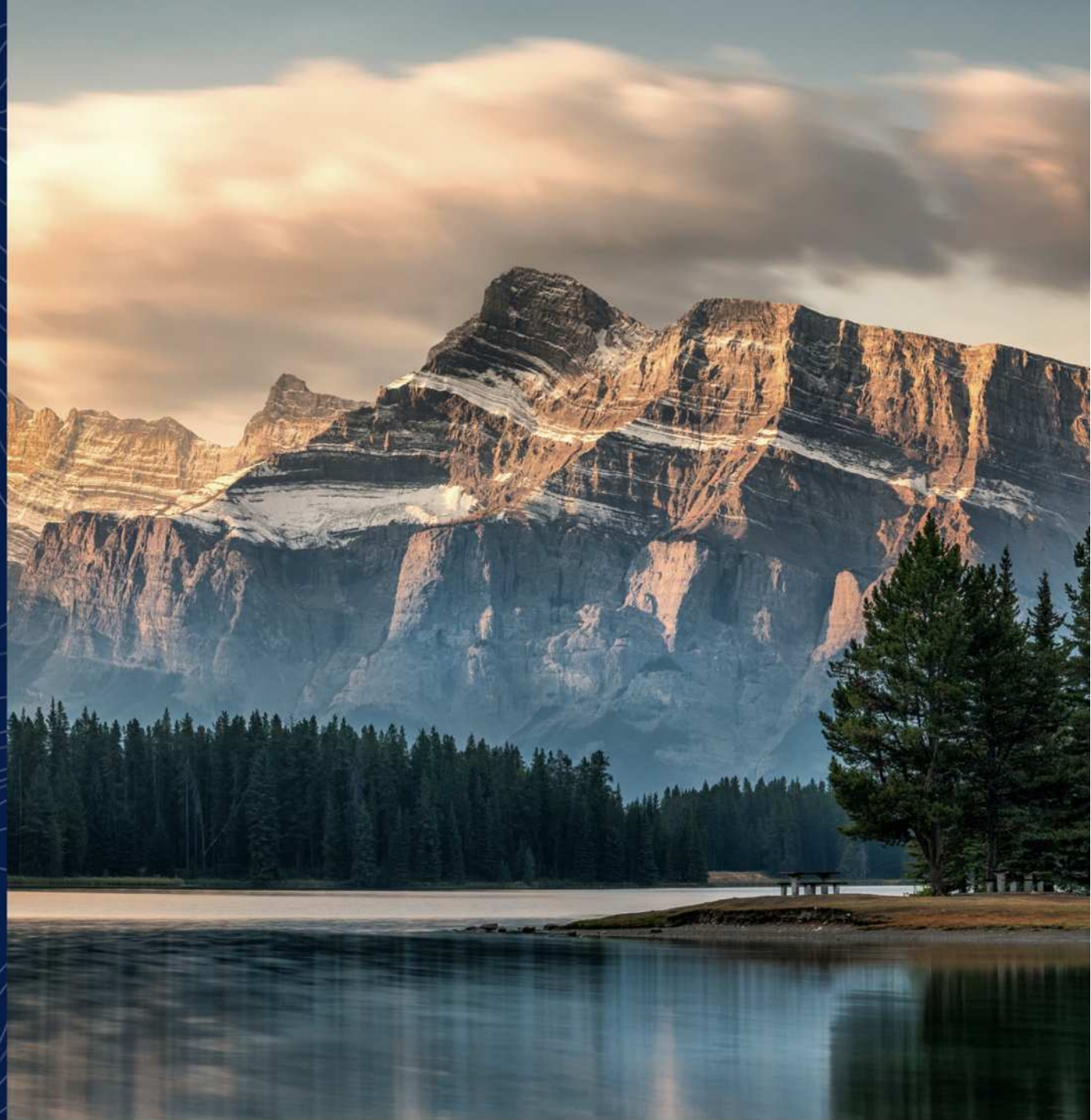


Disclaimer

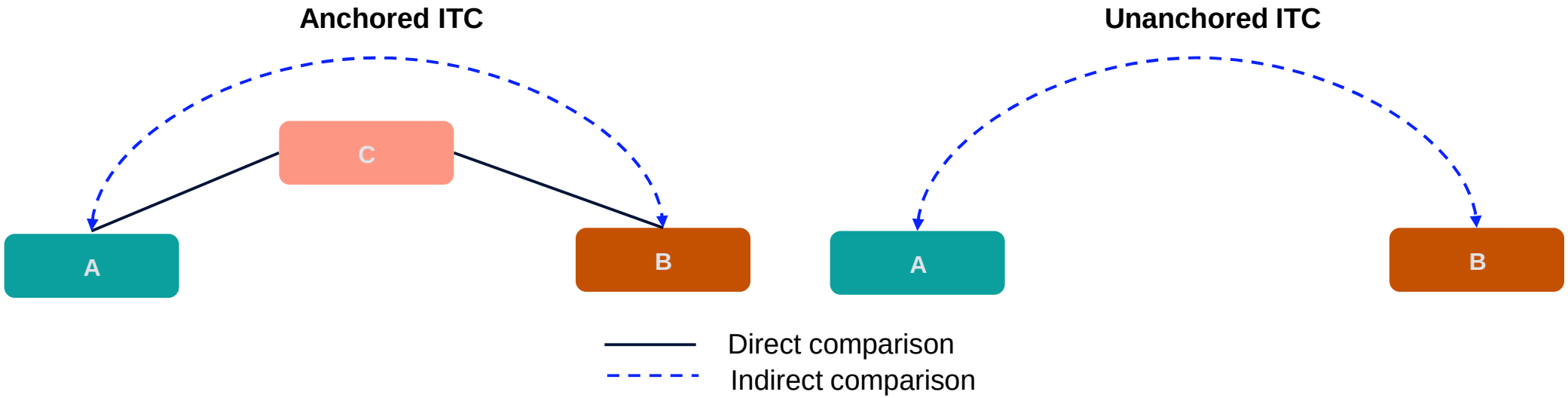
The comments presented here are solely those of the presenter and are not necessarily reflective of the positions, policies or practices of presenter's employers.

Outline

- Introduction
- Methods for Population-adjusted Indirect Comparisons
- Challenges and Considerations for Rare Diseases
- Conclusions

Introduction

- **Anchored Indirect Treatment Comparison (ITC):** connected network with common comparator
- **Unanchored ITC**: lack of common comparator or single-arm studies



- ITCs can be **unadjusted or adjusted**
  - Unadjusted ITCs: do not explicitly adjust for cross-study differences in baseline covariates
  - Adjusted ITCs: explicitly adjust for cross-study differences in baseline covariates

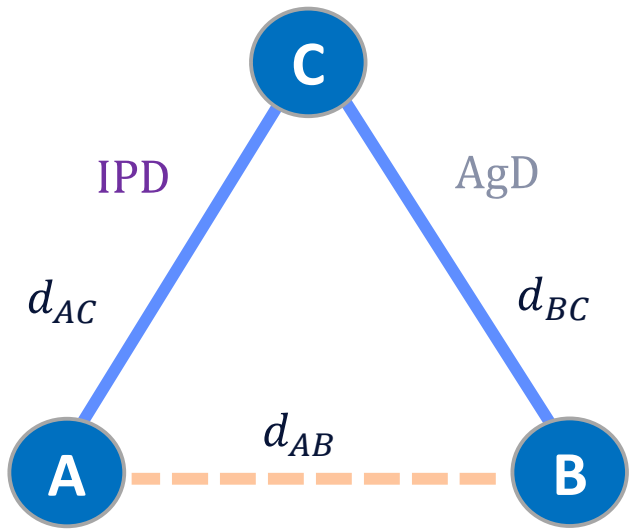
Population-adjusted Indirect Comparisons (PAICs)

- **Background**
  - No head-to-head trials
  - Mixture of individual patient data (IPD) and aggregate data (AgD)
    - Company: IPD, Comparator: AgD

- **Population-adjusted Indirect Comparisons**: use the available IPD to adjust for between-trial imbalances in the distribution of observed covariates
  - Adjustment
    - Anchored ITC: adjust **effect modifiers**
    - Unanchored ITC: adjust both **effect modifiers** and **prognostic variables**
  - Popular methods
    - Matching Adjusted Indirect Comparisons (MAIC)
    - Simulated Treatment Comparisons (STC)

Prognostic variable: a covariate that influences the **outcomes** equally on all treatments. Impacts the **absolute effect**, but not the relative effect.
Effect modifier: a covariate that influences the **treatment effect**. Impacts the **relative effect**.

Anchored MAIC



Direct comparison

Indirect comparison

Setting

- Pairwise comparison of two treatments
- Mixed data: AC trial with IPD; BC trial with AgD

Method

- **Assumption**
  - Conditional constancy of relative effects: all **effect modifiers** known and adjusted for
- **Propensity score weighting-based method**
  - Reweight individuals from the AC trial to match covariate distribution with the BC trial
  - Take a weighted mean to estimate mean outcomes on A and C in the BC trial
  - Then estimate the relative treatment effect of A vs. B in the BC population

Anchored MAIC: Practical Steps

Step 1: Compare the baseline characteristics of the IPD trial against the AgD trial

Step 2: Reweight patients in the IPD trial (AC trial) to match baseline characteristics in AgD trial (BC trial)

- Create a logistic propensity score model for trial allocation

$$log\,(w_i) = \alpha_0 + X_i\alpha$$

- Weights w_i represents the inverse of odds of being enrolled in IPD trial vs. AgD trial
- Weights can be estimated by the **method of moments** (Signorovitch et. al 2012)
  - Set the weights so that the mean [and SDs, if continuous] of covariates are matched

Step 3: Predict outcomes on treatment A and C in the BC population by reweighting the outcomes of the individuals of AC population

$$\hat{Y}_{t(BC)} = \frac{\sum_{i=1}^{N_{t(AC)}} Y_{it(AC)} w_{it}}{\sum_{i=1}^{N_{t(AC)}} w_{it}}, \qquad \text{where t} = \text{A, C}$$

Step 4: Obtain the relative treatment effect of A vs. B in the BC population, using the prediction from step 3 and reported aggregate data for BC trial

$$\hat{d}_{AB(BC)} = \hat{d}_{BC(BC)} - \hat{d}_{AC(BC)} = \left(g\left(\bar{Y}_{C(BC)}\right) - g\left(\bar{Y}_{B(BC)}\right)\right) - \left(g\left(\hat{Y}_{C(BC)}\right) - g\left(\hat{Y}_{A(BC)}\right)\right)$$

Step 5: Calculate standard error, usually robust sandwich estimator

Step 6: Present the distribution of estimated weights and effective sample size (ESS): $ESS = \frac{\left(\sum_i w_i\right)^2}{\left(\sum {w_i}^2\right)}$

Signorovitch et al. Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research. Value in Health. 2012;15:940-7.

Unanchored MAIC: Practical Steps

Assumption:

Conditional constancy of absolute effects: all **effect modifiers** and **prognostic variables** known and adjusted for

Steps:

Similar as anchored comparison

Step 1: Compare the baseline characteristics of the IPD trial against the AgD trial

Step 2: Reweight patients in the IPD trial to match baseline characteristics in AgD trial

- Create a logistic propensity score model for trial allocation including all effect modifiers and prognostic variables

$$log\,(w_i) = \alpha_0 + X_i\alpha$$

- Weights w_i can be estimated similarly as in anchored case

Step 3: Predict outcomes on treatment A in the Study B population by reweighting the outcomes of the individuals of A population

$$\hat{Y}_{A(B)} = \frac{\sum_{i=1}^{N_{A(A)}} Y_{i(A)} w_{it}}{\sum_{i=1}^{N_{A(A)}} w_i},$$

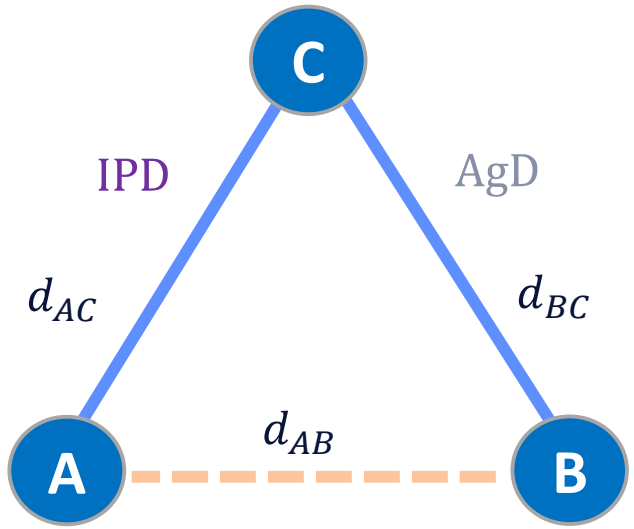
Step 4: Obtain the unanchored indirect comparison in Study B population, using the prediction from step 3 and reported aggregate data for B trial

$$\hat{d}_{AB(B)} = \hat{d}_{B(B)} - \hat{d}_{A(B)} = g\left(\bar{Y}_{B(B)}\right) - g\left(\hat{Y}_{A(B)}\right)$$

Step 5: Calculate standard error, usually robust sandwich estimator

Step 6: Present the distribution of estimated weights and ESS: $ESS = \frac{\left(\sum_i w_i\right)^2}{\left(\sum {w_i}^2\right)}$

Anchored STC



Direct comparison

Indirect comparison

Setting

- Pairwise comparison of two treatments
- AC trial with IPD; BC trial with AgD

Method

- **Assumption**
  - Conditional constancy of relative effects: all **effect modifiers** known and adjusted for
- **Outcome regression-based method**
  - Create an outcome regression model based on the IPD of the AC trial
  - Use the coefficients of fitted model to predict mean outcomes on treatments A and C in the BC population
    - Standard method: “plugging-in” mean approach
    - Computational method: simulate individual-level covariates
  - Then estimate the relative treatment effect of A vs. B in the BC population

Anchored STC: Practical Steps of Standard Method

Step 1: Compare the baseline characteristics of the IPD trial against the AgD trial

Step 2: Fit an outcome regression model based on the IPD of the AC trial

$$g(\mu_t) = \beta_0 + X\beta_1 + (\beta_A + X^{EM}\beta_2)1(t = A)$$

Where μ_t is the expected outcome of treatment t, $g(\cdot)$ is a suitable link function, β_1 is a vector of coefficients for prognostic variables, β_2 is a vector of interaction coefficients for effect modifiers X^{EM} , and β_A is conditional treatment effect for A vs. C

Step 3: Substitute in mean covariate values in the BC trial to predict mean outcomes on treatments A and C in the BC population

$$g\left(\hat{Y}_{A(BC)}\right) = \hat{\beta}_0 + \bar{X}_{(BC)}\hat{\beta}_1 + \hat{\beta}_A + \bar{X}^{EM}_{(BC)}\hat{\beta}_2$$

$$g\left(\hat{Y}_{C(BC)}\right) = \hat{\beta}_0 + \bar{X}_{(BC)}\hat{\beta}_1$$

Step 4: Obtain the relative treatment effect of A vs. B in the BC population, using the prediction from step 3 and reported aggregate data for BC trial

$$\hat{d}_{AB(BC)} = \hat{d}_{BC(BC)} - \hat{d}_{AC(BC)} = g\left(\bar{Y}_{C(BC)}\right) - g\left(\bar{Y}_{B(BC)}\right) - \left(g\left(\hat{Y}_{C(BC)}\right) - g\left(\hat{Y}_{A(BC)}\right)\right)$$

Step 5: Calculate standard error

Anchored STC: Practical Steps of Computational Method

- $g(\cdot)$ is identity link function
  - "Plugging-in" mean approach: OK

- $g(\cdot)$ is non-identity link function
  - "Plugging-in" mean approach: aggregation bias 

Step 1 and 2: The same as standard method

Step 3: Simulate individual-level covariates for BC trial, e.g., using a copula distribution, and then average the predictions of these individuals

Step 4: Predicted mean outcomes on treatments A and C in the BC population

$$\hat{Y}_{A(BC)} = \frac{1}{N}\sum_{j=1}^{N} g^{-1}\left(\hat{\beta}_0 + X_j^*\hat{\beta}_1 + \hat{\beta}_A + X_j^{*(EM)}\hat{\beta}_2\right), \hat{Y}_{C(BC)} = \frac{1}{N}\sum_{j=1}^{N} g^{-1}\left(\hat{\beta}_0 + X_j^*\hat{\beta}_1\right)$$

General formula for $\hat{d}_{AC(BC)}$ is

$$\hat{d}_{AC(BC)} = g\left(\frac{1}{N}\sum_{j=1}^{N} g^{-1}\left(\hat{\beta}_0 + X_j^*\hat{\beta}_1\right)\right) - g\left(\frac{1}{N}\sum_{j=1}^{N} g^{-1}\left(\hat{\beta}_0 + X_j^*\hat{\beta}_1 + \hat{\beta}_A + X_j^{*(EM)}\hat{\beta}_2\right)\right)$$

Step 5: Calculate standard error

Unanchored STC: Practical Steps

Assumption:

Conditional constancy of absolute effects: all **effect modifiers** and **prognostic variables** known and adjusted for

Steps:

Similar as anchored comparison for both methods

Step 1: Compare the baseline characteristics of the IPD trial against the AgD trial

Step 2: Fit an outcome regression model based on the IPD of the A trial, including all effect modifiers and prognostic variables

$$g(\mu_A) = \beta_0 + X\beta_1$$

Step 3: Predict the treatment effect for Study B population using either standard method or computation method

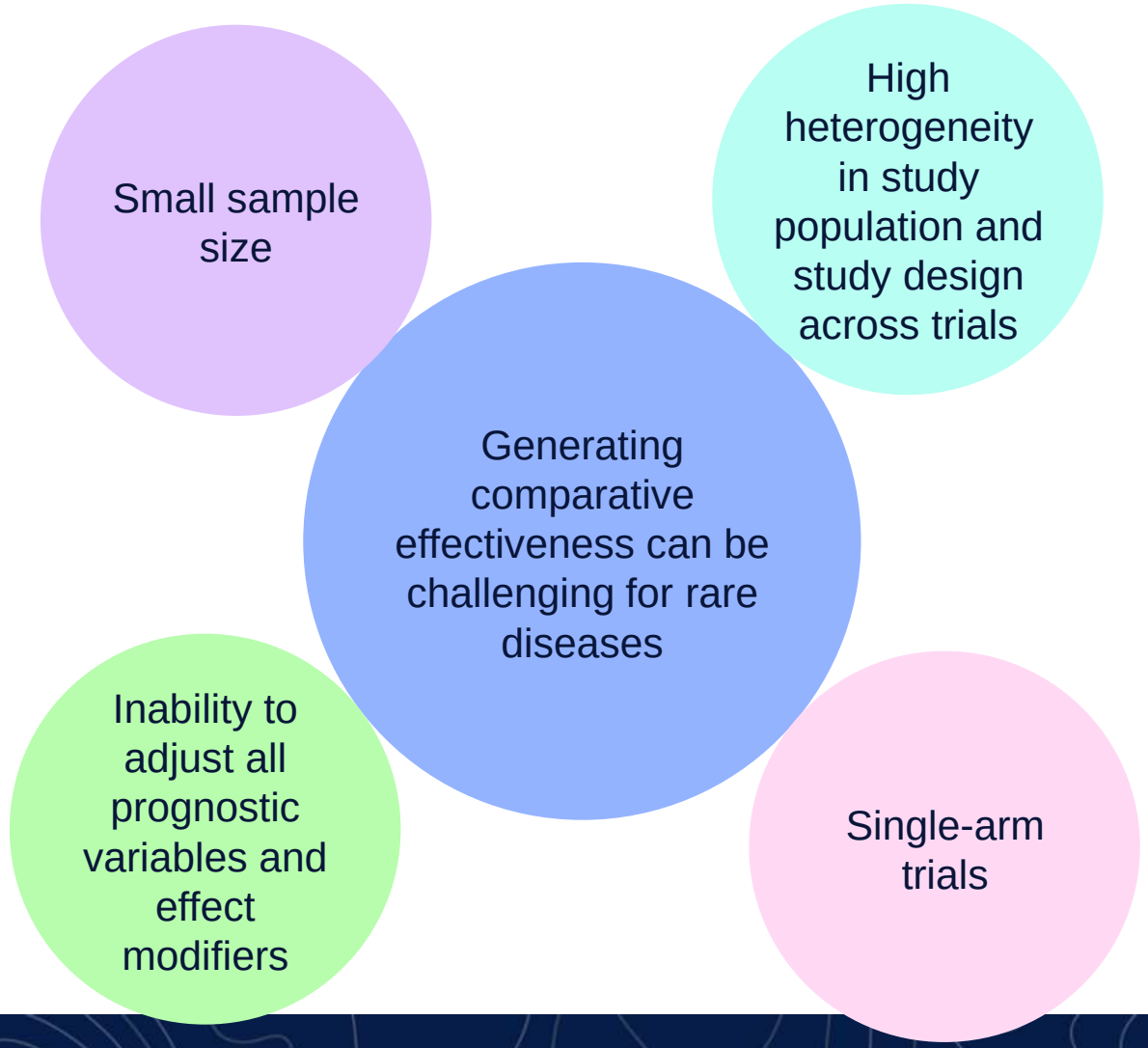
$$\hat{d}_{A(B)} = g\left(\hat{Y}_{A(B)}\right)$$

Step 4: Obtain the unanchored indirect comparison in Study B population, using the prediction from Step 3 and reported aggregated data for Study B

$$\hat{d}_{AB(B)} = \hat{d}_{B(B)} - \hat{d}_{A(B)} = g\left(\bar{Y}_{B(B)}\right) - g\left(\hat{Y}_{A(B)}\right)$$

Step 5: Calculate standard error

Challenges for Rare Diseases



MAIC

- MAIC using small trials may be limited by the number of covariates that can be included in the weighting model
- Poor precision when overlap is limited and small effective sample size after reweighting; extreme weights lead to high uncertainty in estimates
- Feasible weighting solution may not exist
- Limitations of unanchored MAIC

STC

- Sample size may be too small to fit a robust regression model
- Regression model may only be feasible to adjust for limited covariates
- Large amount of uncertainty in predictions
- Limitations of unanchored STC

Alternative Methods to Address Challenges: Two Stage MAIC

- **First stage:** fit the propensity score model for the **treatment assignment mechanism** in the IPD study (AC)

$$logit(e_i) = \beta_0 + X_i\beta_1$$

  Estimate $\hat{e}_i$ as the probability of subject i being assigned to treatment A

- **Second stage:** fit the propensity score model for **trial assignment mechanism** and calculate the weights ($\widehat{w}_i$) that balance the covariates between the AC trial and the BC trial, which can be MAIC weights by any method

  Compute the final weights:

$$\widehat{\omega}_i = \frac{t_i\widehat{w}_i}{\hat{e}_i} + \frac{(1-t_i)\widehat{w}_i}{1-\hat{e}_i}$$

  Where t_i=1 if assigned to treatment A and t_i=0 if assigned to treatment C

- **Limitation**
  - It depends on a treatment assignment model and therefore cannot be applied in unanchored scenarios

Remiro-Azócar, A., 2022. Two stage matching-adjusted indirect comparison. BMC medical research methodology,22(1), p.217.

Alternative Methods to Address Challenges: Weight Truncation

- Extreme weights can be controlled by capping the highest estimated weights at a specified percentile
- The appropriate truncation threshold should be chosen empirically for each analysis level on a case-by-case basis, e.g., by progressively truncating the weights
- Bias-variance trade-off: Lowering the truncation point often increases precision (lower variance) but introduces bias
- In transportability/generalizability studies, a 95th percentile cutoff is frequently used. Using lower percentiles further decreases variance but can substantially increase bias and shift the target population or estimand
- Limitations
  - Shifts the target estimand definition (population or analysis set attribute)
  - Selecting a cutoff threshold often involves arbitrary ad hoc decisions

Alternative Methods to Address Challenges: Variance Reduction

MAIC with Largest ESS (Jackson et.al, 2021)

- Estimate the weights that match the moments of covariates and have the largest possible ESS under the restriction of all weights being non-negative
- Weight can be solved by

$$\min_{\boldsymbol{w}} \left\{ \sum_i w_i^2 \right\} \text{ subject to } \sum_i w_i \boldsymbol{X_i} = \boldsymbol{\mu} \text{ and } \sum_i w_i = 1.$$

- Minimizes weight dispersion, resulting in more stable weights that enhance precision, but this stability comes at the expense of introducing bias

Reduce the Number of Moment-balancing Conditions

- Exclude less influential covariates
- Exclude higher-order moments, e.g., only balance means and not variances
- Promotes greater overlap and reduces the likelihood of extreme weights, resulting in less severe reductions to effective sample size and precision
- However, it also leads to residual bias (Vo 2023, Remiro-Azócar 2024)

Jackson et.al, 2021. Alternative weighting schemes when performing matching-adjusted indirect comparisons. Res Synth Methods.
Remiro-Azocar, Advanced methods for matching adjusted indirect comparison, ISPOR 2024
Vo, T.T., 2023. A cautionary note on the use of G-computation in population adjustment. Research Synthesis Methods, 14(3), pp.338-341

Simulation Evaluation of Alternative Methods

Simulation evaluation by Remiro-Azócar (2022)

Data generating and setting

- Anchored comparison between two RCTs
- Continuous outcome, linear outcome generating model
- Effect measure: mean difference
- 3 strongly prognostic and effect-modifying covariates simulated from a multivariate normal distribution
- Small sample size for IPD trial (n=140, 200) & varying overlap across trials

Methods evaluated

- Standard MAIC
- Two-stage MAIC (2SMAIC)
- MAIC with weight truncation (T-MAIC), capping the estimated weights at the 95th percentile
- 2SMAIC combined with weight truncation (T-2SMAIC), capping the estimated weights at the 95th percentile

Main conclusions

Two-stage MAIC

- Is effective when the IPD trial sample size is small, as it helps control for chance imbalances in prognostic baseline covariates across study arms
- Performance is limited when there is poor overlap between target populations and when estimated weights are highly extreme

MAIC with Weight Truncation

- When covariate overlap is strong, truncation yields modest gains in precision and efficiency, but introduces bias
- When overlap is poor, truncation provides substantial improvements in precision and efficiency but results in considerable bias

Two-stage MAIC with Weight Truncation

- The combination of a two-stage approach with truncation delivers the highest enhancements in precision and efficiency overall

Remiro-Azócar, A., 2022. Two stage matching-adjusted indirect comparison. BMC medical research methodology,22(1), p.217.
Remiro-Azocar, Advanced methods for matching adjusted indirect comparison, ISPOR 2024

Other Practical Considerations to Conduct PAICs

- **Prognostic variables and effect modifiers**
  - The identification process of effect modifiers and prognostic variables can be time consuming, and requires collaboration between clinical expertise and statistical analysis
  - The reporting of the analyses should detail how prognostic variables and effect modifiers were identified a priori and specify whether these variables were available in the trials being compared
  - MAICs or STCs using small trials in rare disease may be limited by the number of variables that can be included in model. Under these conditions, it is advisable to prioritize inclusion of the most impactful effect modifiers and prognostic variables
- **Comparability of trials included**
  - The included trials should be comparable with respect to inclusion/exclusion criteria, baseline characteristics, study design, definitions and assessment of outcomes
- **Sensitivity analyses**
  - It is essential to include multiple approaches as sensitivity analyses since ITC inherently carry a high risk of bias regardless of the specific method employed

Conclusions

- PAICs are playing an important role in quantifying the relative effectiveness of different health interventions
- PAICs face significant challenges due to the inherent characteristics of rare disease, which may lead to evidence that is inconclusive or unsuitable for informing robust decision-making
- Advanced methods have been proposed and may improve the precision and efficiency of traditional methods. Continued methodological refinement are crucial for developing reliable evidence
- It is important to consider multiple approaches as sensitive analyses
- Careful planning, rigorous reporting, and thoughtful selection of appropriate methods are essential to minimize bias and maximize validity

Reference

- Jackson et.al, 2021. Alternative weighting schemes when performing matching-adjusted indirect comparisons. Res Synth Methods.
- Remiro-Azócar, A., 2022. Two stage matching-adjusted indirect comparison. BMC medical research methodology,22(1), p.217.
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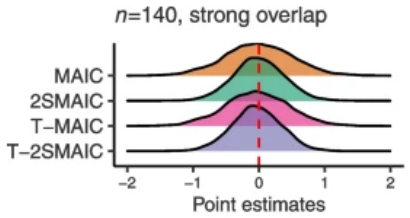
- Vo, T.T., 2023. A cautionary note on the use of G-computation in population adjustment. Research Synthesis Methods, 14(3), pp.338-341

Thank you !

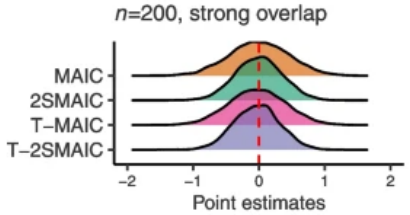
Simulation Evaluation of Alternative Methods

Performance measures:

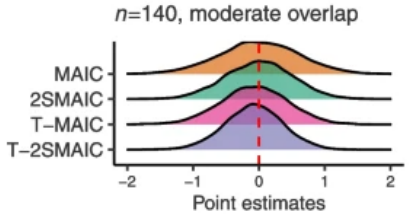
- Bias
- Empirical coverage rate of the 95% confidence interval
- Empirical standard error (ESE)
- Mean square error (MSE)



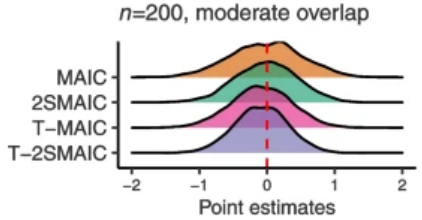
Method	Bias	Cov	ESE	MSE
MAIC	−0.006 (0.007)	0.935 (0.003)	0.516 (0.005)	0.266 (0.005)
2SMAIC	−0.001 (0.005)	0.955 (0.003)	0.386 (0.004)	0.149 (0.003)
T–MAIC	−0.031 (0.007)	0.943 (0.003)	0.489 (0.005)	0.240 (0.005)
T–2SMAIC	−0.035 (0.005)	0.954 (0.003)	0.371 (0.004)	0.139 (0.003)



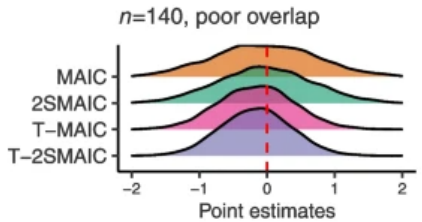
Method	Bias	Cov	ESE	MSE
MAIC	0.003 (0.006)	0.949 (0.003)	0.453 (0.005)	0.205 (0.004)
2SMAIC	−0.001 (0.005)	0.953 (0.003)	0.356 (0.004)	0.127 (0.003)
T–MAIC	−0.023 (0.006)	0.951 (0.003)	0.430 (0.004)	0.186 (0.004)
T–2SMAIC	−0.030 (0.005)	0.953 (0.003)	0.342 (0.003)	0.118 (0.002)



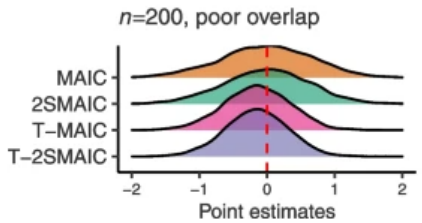
Method	Bias	Cov	ESE	MSE
MAIC	−0.002 (0.008)	0.932 (0.004)	0.600 (0.006)	0.361 (0.007)
2SMAIC	0.001 (0.007)	0.946 (0.003)	0.514 (0.005)	0.264 (0.005)
T–MAIC	−0.070 (0.007)	0.952 (0.003)	0.509 (0.005)	0.264 (0.005)
T–2SMAIC	−0.076 (0.006)	0.951 (0.003)	0.435 (0.004)	0.195 (0.004)



Method	Bias	Cov	ESE	MSE
MAIC	−0.014 (0.007)	0.938 (0.003)	0.530 (0.005)	0.281 (0.005)
2SMAIC	−0.008 (0.006)	0.944 (0.003)	0.458 (0.005)	0.209 (0.004)
T–MAIC	−0.083 (0.006)	0.948 (0.003)	0.448 (0.004)	0.207 (0.004)
T–2SMAIC	−0.085 (0.006)	0.951 (0.003)	0.389 (0.004)	0.159 (0.003)



Method	Bias	Cov	ESE	MSE
MAIC	−0.041 (0.011)	0.900 (0.004)	0.767 (0.008)	0.589 (0.012)
2SMAIC	−0.031 (0.010)	0.917 (0.004)	0.703 (0.007)	0.495 (0.010)
T–MAIC	−0.157 (0.008)	0.939 (0.003)	0.563 (0.006)	0.342 (0.007)
T–2SMAIC	−0.160 (0.007)	0.939 (0.003)	0.519 (0.005)	0.295 (0.006)



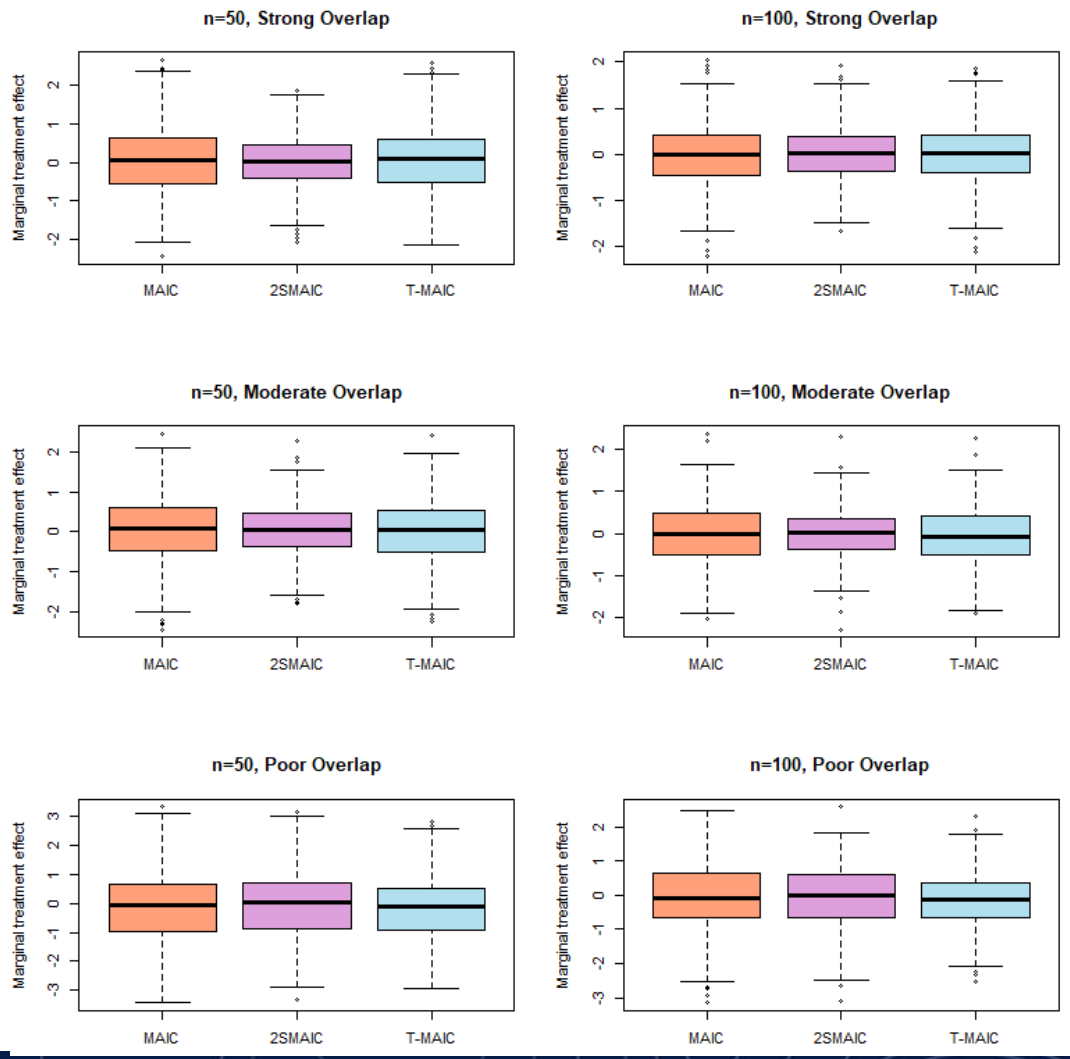
Method	Bias	Cov	ESE	MSE
MAIC	−0.010 (0.010)	0.911 (0.004)	0.677 (0.007)	0.459 (0.009)
2SMAIC	−0.007 (0.009)	0.926 (0.004)	0.627 (0.006)	0.393 (0.008)
T–MAIC	−0.149 (0.007)	0.939 (0.003)	0.490 (0.005)	0.263 (0.005)
T–2SMAIC	−0.153 (0.006)	0.937 (0.003)	0.458 (0.005)	0.233 (0.005)

Remiro-Azócar, A., 2022. Two stage matching-adjusted indirect comparison. BMC medical research methodology,22(1), p.217.

Simulation Evaluation of Alternative Methods

Performance measures:

- Bias
- Empirical coverage rate of the 95% confidence interval
- Empirical standard error (ESE)
- Mean square error (MSE)



n=50, Strong Overlap

Method	Bias	Cov	ESE	MSE
MAIC	0.027 (0.038)	0.940 (0.011)	0.849 (0.027)	0.720 (0.045)
2SMAIC	0.024 (0.029)	0.954 (0.009)	0.658 (0.021)	0.432 (0.028)
T-MAIC	0.052 (0.036)	0.948 (0.010)	0.810 (0.026)	0.657 (0.042)

n=50, Moderate Overlap

Method	Bias	Cov	ESE	MSE
MAIC	0.084 (0.036)	0.952 (0.010)	0.806 (0.025)	0.655 (0.041)
2SMAIC	0.037 (0.028)	0.978 (0.007)	0.631 (0.020)	0.398 (0.026)
T-MAIC	0.056 (0.034)	0.960 (0.009)	0.763 (0.024)	0.584 (0.036)

n=50, Poor Overlap

Method	Bias	Cov	ESE	MSE
MAIC	-0.137 (0.055)	0.892 (0.014)	1.197 (0.039)	1.148 (0.09)
2SMAIC	-0.081 (0.050)	0.918 (0.013)	1.083 (0.036)	1.176 (0.073)
T-MAIC	-0.179 (0.047)	0.921 (0.012)	1.013 (0.033)	1.056 (0.067)

n=100, Strong Overlap

Method	Bias	Cov	ESE	MSE
MAIC	-0.016 (0.030)	0.944 (0.010)	0.676 (0.021)	0.456 (0.030)
2SMAIC	0.004 (0.026)	0.956 (0.009)	0.575 (0.018)	0.329 (0.021)
T-MAIC	0.006 (0.029)	0.952 (0.010)	0.651 (0.021)	0.423 (0.027)

n=100, Moderate Overlap

Method	Bias	Cov	ESE	MSE
MAIC	-0.034 (0.031)	0.958 (0.009)	0.690 (0.022)	0.476 (0.029)
2SMAIC	-0.016 (0.025)	0.968 (0.008)	0.554 (0.018)	0.307 (0.023)
T-MAIC	-0.062 (0.030)	0.956 (0.009)	0.667 (0.021)	0.447 (0.028)

n=100, Poor Overlap

Method	Bias	Cov	ESE	MSE
MAIC	-0.033 (0.042)	0.902 (0.013)	0.950 (0.030)	0.902 (0.058)
2SMAIC	-0.024 (0.039)	0.914 (0.013)	0.879 (0.028)	0.772 (0.048)
T-MAIC	-0.139 (0.034)	0.940 (0.011)	0.755 (0.024)	0.588 (0.038)