MATCHING-ADJUSTED INDIRECT COMPARISON (MAIC) IN HTA AND ITS APPLICATION USING SAS PROCEDURES

PhUSE Single Day Events

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Today's objectives

- Present concepts of the ITC using the MAIC methodology using SAS™ procedures
  - With or without anchor (common comparator).
- Demonstrate an application of MAIC to an example in oncology
  - Comparing overall survival curves of a new therapy compared to standard therapy.
- Introduce a generalized method to run such analyses
  - Using SAS v9.3
  - Performed in a straightforward manner, within existing procedures without using SAS/IML.

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Agenda / TOC

1. Background and Introduction
2. Methods and Concepts
3. Implementation (SAS)
4. Oncology Example
5. Results
6. Conclusions
7. Limitations
8. References

Abbreviations

Abbreviation	Description
ITC	Indirect Treatment Comparison
MAIC	Matching Adjusted Indirect Comparison
HTA	Health Technology Assessment
IPD	Individual Patient Data
AD	Aggregate Data
NICE	National Institute for Health and Care Excellence
G-BA	Gemeinsamer Bundesausschuss
SLR	Systematic Literature Review

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Background and Introduction

- In support of HTA submissions,
  - Critical to compare a new treatment to the standard treatment.
  - In the absence of direct comparisons, ITC becomes increasingly important.
- Several HTA agencies documented their interest in obtaining results from such analyses
  - In the absence of direct comparisons (NICE-UK[1], G-BA-Germany[2])

- Naïve ITC based on treatments arms from different trials is prone to bias
  - Because of cross-trial differences in study populations and characteristics.
  - ITC (Bucher) without adjustment is still acceptable (e.g., for Germany,…)

- When the interest is in comparing two treatments, one with IPD and one with published AD → MAIC method represents an attractive option[3]

1. Phillippo DM et al. NICE DSU technical support document 18: methods for population-adjusted indirect comparisons in submissions to NICE. December 2016.
2. Dossier zur Nutzenbewertung gemäß § 35a SGB V. Modul 4. 16-03-2018.
3. Signorovitch JE et al. Matching-Adjusted Indirect Comparisons: a new tool for timely comparative effectiveness research. Value in Health 15(2012) 940-947.

Direct vs. Indirect Treatment Comparisons

- Presence of head-to-head randomized trials
  - → Direct comparison
- Absence of head-to-head randomized trials AND connected network with a common comparator
  - → Anchored ITC should be considered
  - Without adjustment → naïve comparison (e.g., Bucher)
  - With adjustment → adjust for all effect modifiers
- Absence of connected network (no common comparator) or only single-arm studies available
  - Unanchored ITC is the only option
  - Adjustment for all effect modifiers and prognostic variables
- Unanchored ITCs require much stronger assumptions → Anchored ITCs are always preferred

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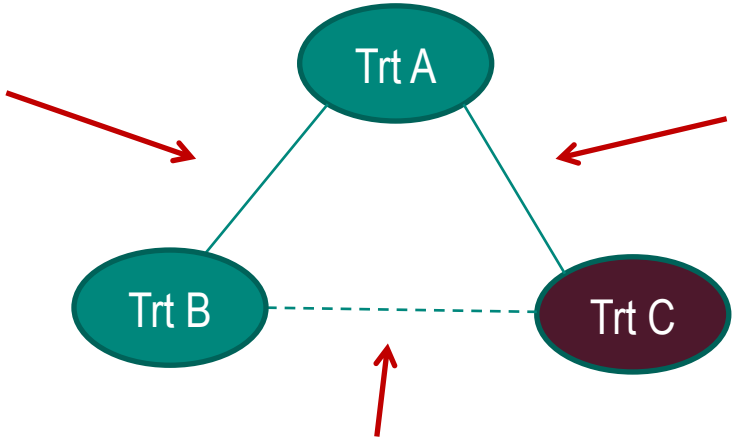
MAIC - Mixed Data

- Ideal scenario: full individual patient data (IPD) → "Gold standard" – IPD meta-regression
- Common scenario: limited IPD → Several recent methods make use of mixed data

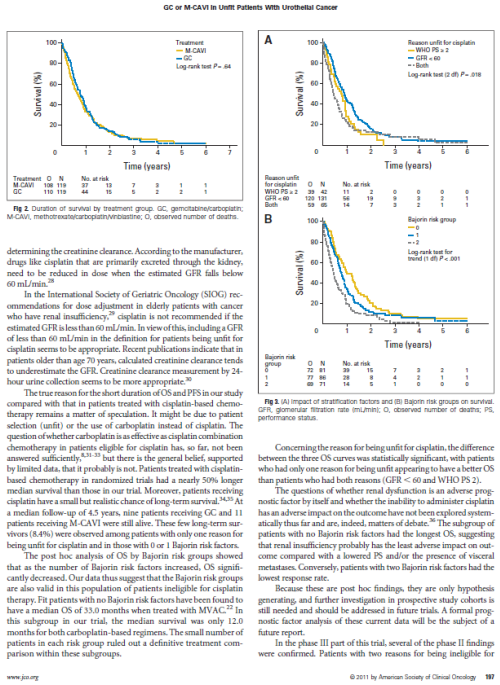
AB trial: IPD

Obs	prev	move	date	high	low	open	close	datechar	dateref
1	.	Up	20SEP16	$781.37	$776.00	$776.00	$780.22	20SEP16	20SEP16
2	780.22	Up	21SEP16	$790.69	$779.01	$783.25	$789.74	21SEP16	
3	789.74	Up	22SEP16	$805.88	$794.27	$794.27	$804.70	22SEP16	
4	804.70	Up	23SEP16	$807.75	$802.12	$803.13	$805.75	23SEP16	
5	805.75	Down	26SEP16	$805.93	$797.14	$801.80	$799.16	26SEP16	
6	799.16	Up	27SEP16	$816.64	$801.11	$801.85	$816.11	27SEP16	
7	816.11	Up	28SEP16	$830.14	$817.03	$818.00	$828.72	28SEP16	
8	828.72	Up	29SEP16	$837.50	$824.63	$828.26	$829.05	29SEP16	
9	829.05	Up	30SEP16	$839.95	$832.40	$832.61	$837.31	30SEP16	
10	837.31	Down	03OCT16	$839.86	$831.25	$836.00	$836.74	03OCT16	03OCT16
11	836.74	Down	04OCT16	$842.36	$830.26	$840.91	$834.03	04OCT16	



Comparison of interest: Trt B vs. Trt C

AC trial: aggregate data


GC or M-CAVI in Unfit Patients With Urothelial Cancer

determining the creatinine clearance. According to the manufacturer, drugs like cisplatin that are primarily excreted through the kidney, need to be reduced in dose when the estimated GFR falls below 60 mL/min.[28]

In the International Society of Geriatric Oncology (SIOG) recommendations for dose adjustment in elderly patients with cancer who have renal insufficiency,[29] cisplatin is not recommended if the estimated GFR is less than 60 mL/min. In view of this, including a GFR of less than 60 mL/min in the definition for patients being unfit for cisplatin seems to be appropriate. Recent publications indicate that in patients older than age 70 years, calculated creatinine clearance tends to underestimate the GFR. Creatinine clearance measurement by 24-hour urine collection seems to be more appropriate.[30]

The true reason for the short duration of OS and PFS in our study compared with that in patients treated with cisplatin-based chemotherapy remains a matter of speculation. It might be due to patient selection (unfit) or the use of carboplatin instead of cisplatin. The question of whether carboplatin is as effective as cisplatin combination chemotherapy in patients eligible for cisplatin has, so far, not been answered sufficiently,[8,31-35] but there is the general belief, supported by limited data, that it probably is not. Patients treated with cisplatin-based chemotherapy in randomized trials had a nearly 50% longer median survival than those in our trial. Moreover, patients receiving cisplatin have a small but realistic chance of long-term survival.[34,35] At a median follow-up of 4.5 years, nine patients receiving GC and 11 patients receiving M-CAVI were still alive. These few long-term survivors (8.4%) were observed among patients with only one reason for being unfit for cisplatin and in those with 0 or 1 Bajorin risk factors.

The post hoc analysis of OS by Bajorin risk groups showed that as the number of Bajorin risk factors increased, OS significantly decreased. Our data thus suggest that the Bajorin risk groups are also valid in this population of patients ineligible for cisplatin therapy. Fit patients with no Bajorin risk factors have been found to have a median OS of 33.0 months when treated with MVAC.[22] In this subgroup in our trial, the median survival was only 12.0 months for both carboplatin-based regimens. The small number of patients in each risk group ruled out a definitive treatment comparison within these subgroups.

Concerning the reason for being unfit for cisplatin, the difference between the three OS curves was statistically significant, with patients who had only one reason for being unfit appearing to have a better OS than patients who had both reasons (GFR < 60 and WHO PS 2).

The questions of whether renal dysfunction is an adverse prognostic factor by itself and whether the inability to administer cisplatin has an adverse impact on the outcome have not been explored systematically thus far and are, indeed, matters of debate.[36] The subgroup of patients with no Bajorin risk factors had the longest OS, suggesting that renal insufficiency probably has the least adverse impact on outcome compared with a lowered PS and/or the presence of visceral metastases. Conversely, patients with two Bajorin risk factors had the lowest response rate.

Because these are post hoc findings, they are only hypothesis generating, and further investigation in prospective study cohorts is still needed and should be addressed in future trials. A formal prognostic factor analysis of these current data will be the subject of a future report.

In the phase III part of this trial, several of the phase II findings were confirmed. Patients with two reasons for being ineligible for

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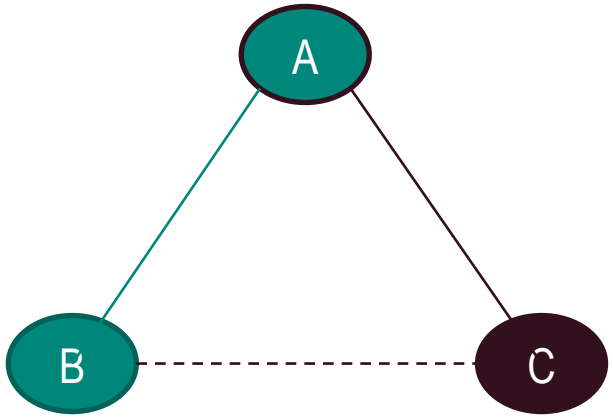
MAIC - Forms of Indirect Comparisons

Anchored



Unanchored

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Overview of MAIC – General Idea

MAIC
Population reweighting
Weight IPD participants to balance covariate distribution with aggregate data trial
Estimate outcomes on A vs. B in the AC trial population (using weights)
Use the above to estimate the treatment effect B vs. C
Check distribution of weights, effective sample size

- AB and AC populations must have sufficient overlap
  - Compare covariate distributions, inclusion/exclusion criteria
- Not the only approaches but presently the most popular

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Overview of MAIC

CAN COMBINE IPD WITH PUBLISHED AD TO:

- **Adjust for cross-trial differences in baseline characteristics**
- Reduce sensitivity to effect measures
- Resolve differences in study outcome definitions
- Allow comparison of clinically relevant dosages
- Deal with incomplete evidence network

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MAIC – General Methods Summary

- For the standard treatment (C):
  - Perform a literature search to identify the studies of interest.
  - Obtain/retrieve summary of baseline characteristics and outcome of interest (e.g. in the published literature)

- Identify the outcome prognostic factors and/or effect modifiers.
  - Perform a literature search for papers identifying prognostic factors and/or effect modifiers to adjust for
    - For an anchored ITC, should adjust for all effect modifiers (in imbalance or not)), but no prognostic variables
    - For an unanchored ITC, should adjust for all effect modifiers AND prognostic variables
  - Consult with clinical experts
  - Document decision in protocol/SAP

- Apply the MAIC methodology*
  - Estimate the weights for IPD to match the summary statistics (e.g., mean or median, proportion) for prognostic factors and/or effect modifiers in AD, using the methods of moments in logistic regression.
  - Perform the appropriate weighted analysis to estimate the treatment effect of B vs. C (e.g., diff in means, RR, OR, HR).

* Signorovitch JE et al. Matching-Adjusted Indirect Comparisons: a new tool for timely comparative effectiveness research. Value in Health 15(2012) 940-947.

MAIC – Methods Summary Specific to Time to Event

- For the standard treatment (C):
  - Perform a literature search to identify the studies of interest.
  - Digitize the published Kaplan-Meier curves and generate pseudo-individual patient data.
  - Pool the pseudo-IPD datasets to form a comparison group.

- Identify the OS prognostic factors and effect modifiers for the specific oncology indication.
  - Same as for any outcome (previous slide):
    - Identification of prognostic factors and/or effect modifiers, consult with clinical experts, document decision in protocol/SAP

- Apply the MAIC methodology*
  - Estimate the weights for IPD to match the summary statistics (e.g., mean or median, proportion) for prognostic factors and effect modifiers in AD, using the methods of moments in logistic regression.
  - Perform a weighted PH regression analysis and estimate the hazard ratio and its standard error (using sandwich estimate).
  - Provide a weighted Kaplan-Meier estimate for the IPD treatment group (B)

* Signorovitch JE et al. Matching-Adjusted Indirect Comparisons: a new tool for timely comparative effectiveness research. Value in Health 15(2012) 940-947.

MAIC – Methods Overview

- Clinical trial selection
  - Systematic literature review, identification of cross-trial differences, availability of IPD assessed (e.g. PICOS criteria)

- Identification of outcomes measures
  - Consider definition of outcomes, assessments schedules, dosages, statistical methods
  - IPD can be re-analyzed to match AD outcome definitions, else could conduct sensitivity analyses

- Matching the trial populations
  - Exclude from ITC, any IPD patients who couldn't have enrolled in published comparator trials
    - E.g. if competitor has inclusion criterion CPS>10% and we have CPS>1%, we should exclude anyone with CPS<=10% from our IPD
  - To adjust for differences in baseline characteristics, patients in trials with IPD have their baseline characteristics weighted such that they match with those reported for trials with AD

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MAIC – Methods Overview

- A form of propensity score weighting
  - Patients in one treatment group (trial with IPD) weighted by inverse odds of being in that group versus the other treatment group (trial with AD)

- Weights can be estimated using generalised methods of moments
  - Can match medians, SDs, where available
  - Cannot use likelihood methods unless IPD available for published study

- Compare outcomes using weighted statistical tests, incorporating weights derived as above
  - Weighted t-tests, Kaplan-Meier tests, log rank tests, risk ratios/differences…

MAIC Concepts and Theory → See Back-up Slides

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MAIC – Implementation

- Code to run such analyses is publically available for the sampling approach, in SAS, and using the exact matching methodology, in R. The exact matching approach using SAS/IML is also referred in several publications.
- No specific procedure currently available but possible to use numerical functionalities within SAS and R

- SAS
  - **PROC NLP (SAS/OR)**
  - PROC SURVEYSELECT (limited functionality)
  - PROC IML, NLPNRA sub-routine (no code publically available)
  - Simulation techniques

- R
  - Code from UK NICE example

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MAIC – Implementation in SAS

General Implementation Steps:

- Import relevant external data (baseline, pseudo-IPD)
- Import data from sponsor and keep relevant variables
- Calculate baseline characteristics for variables before matching
- Calculate mean value of covariates in standard group
- Calculate centered values for covariates in both groups
- Minimization process for matching →
- Calculation of individual weights →
- Calculate baseline characteristics for variables after matching
- Combine sponsor and external data (pseudo) and run analyses (KM, HR)

```
%macro maic(invars=);

      /*Number of variables*/
      %let n_vars=%sysfunc(countw(&invars));

      /*Minimization process for matching*/
      data parl(type=est);
           keep _type_ alpha:;
           _type_='parms';
           %do i=1 %to &n_vars.;
                alpha&i.=1;
           %end;
           output;
      run;

      proc nlp data=in_data inest=parl outest=Oparl;
           min sumexp;
           parms    %do i=1 %to &n_vars.;
                         alpha&i
                    %end;
                    ;
           s=0;

           s+exp(%do i=1 %to &n_vars.;
                         *Name of specific variable;
                         %let bc_var=%scan(&invars.,&i.);
                         alpha&i*&bc_var._cent
                         %if &i<&n_vars. %then +;
                 %end;
                 );
           sumexp=s;
      run;

      data param;
           set oparl;

           if _TYPE_='PARMS';
           keep alpha: ;
      run;

      /*Calculation of individual weights*/
      proc sql;
           create table ind_wt as
                select   *,
                         (exp(%do i=1 %to &n_vars.;
                                   %*Name of specific variable;
                                   %let bc_var=%scan(&invars.,&i.);
                                   p.alpha&i.*t.&bc_var._cent
                                   %if &i<.&n_vars.. %then +;
                              %end;
                              )) as wt
                from     in_data t,
                         param p
                                  ;
      quit;

      /*Calculation of Effective sample size*/
      proc sql;
           select sum(wt)**2/sum(wt**2) as efss
           from ind_wt
           where wt ne .;
      quit;

%mend maic;

%maic(invars=age sex ecog);
```

MAIC Example in Oncology – Unanchored ITC

- Overall Survival for new treatment (A) vs. standard treatment (B)

- SLR originally conducted by vendor for Sponsor-customer dossier submission
  - Included 6 standard treatment (B) studies
    - Subsequently identified 2 studies relevant to MAIC analysis
  - Vendor is digitizing these published KM curves
    - Obtaining patient-level data, via an algorithm

- Work with Clinical & Sponsor-customer to identify:
  - Differences in inclusion/exclusion criteria
  - Potential effect modifiers & prognostic factors
    - Aligning these with available information

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MAIC Example in Oncology – Unanchored ITC

- Run matching algorithm/procedure to derive weights for IPD sponsor trial patients
  - → Baseline characteristics & demographics match those for published data

- Present baseline characteristics before and after matching
- Present KM curve for the unadjusted and adjusted new treatment (A) together with standard therapy (B)
- Report the HR (95% CI), preferably for both naive (before matching) and adjusted (after matching) comparisons

- Analyse weighted sponsor IPD data vs. published data
  - Obtain HR (95% CI)

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MAIC Example in Oncology – Unanchored ITC Results

	Before Matching		After Matching	
Baseline Characteristics	**A (N=370)**	**B (N=175)**	**A (N=143.95[b])**	**B (N=175)**
Age (median)	73.0	71.6	**71.6**	71.6
Sex (male, %)	77.3	78.8	**78.8**	78.8
ECOG Score (%)				
0	21.6	16.0	**16.0**	16.0
1	36.2	38.9	**38.9**	38.9
2+	42.2	45.1	**45.1**	45.1
Visceral Metastases (%)	86.1	45.1	**45.1**	45.1
Liver Metastases (%)	20.8	17.2	**17.2**	17.2

b: Effective sample size computed as the square of the summed weights divided by the sum of the squared weights*

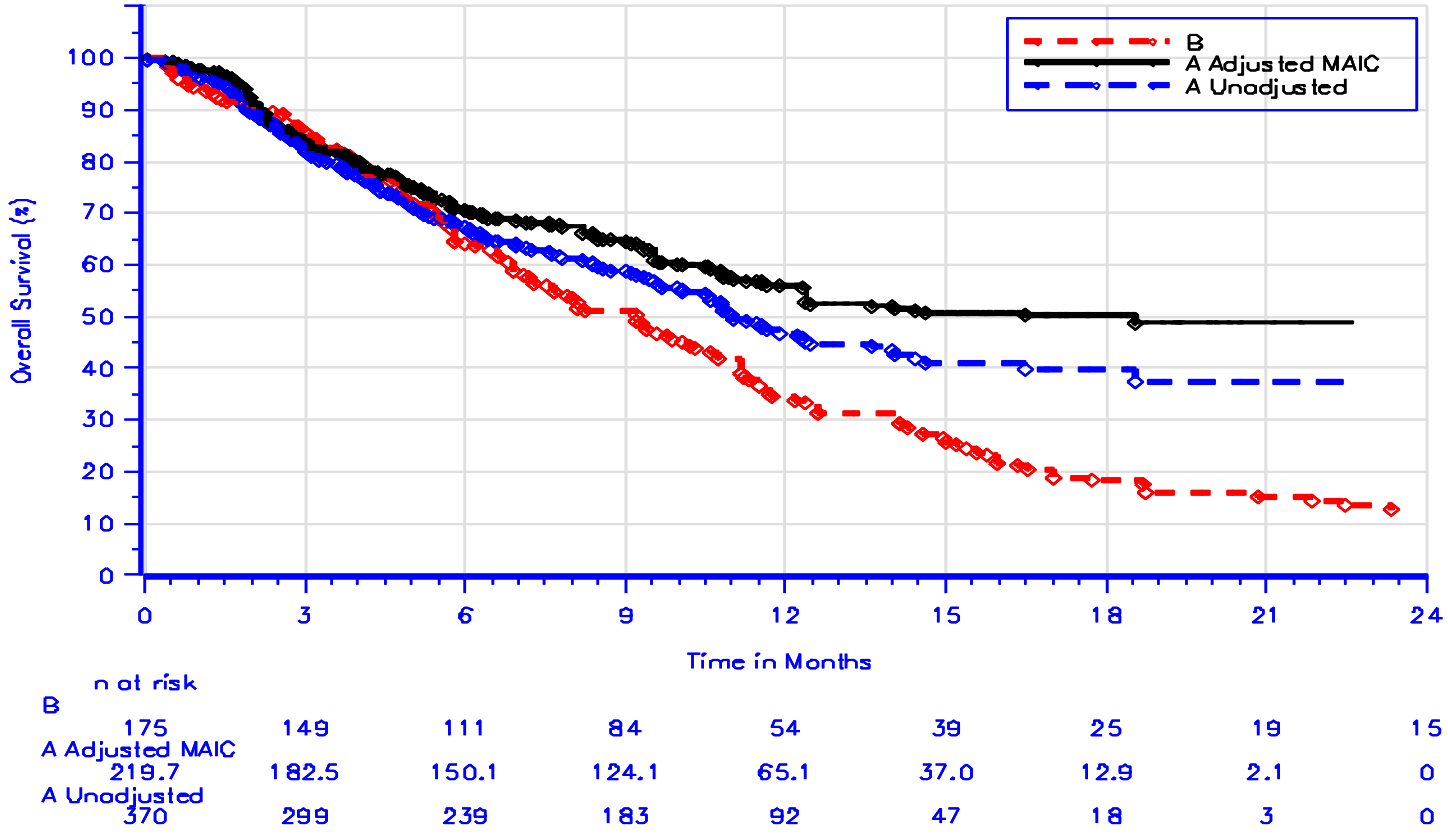
- Large difference in percentages of subjects with baseline visceral metastases was observed before matching.
- Likely a contributory factor to the ESS of A being considerably smaller (143.9) than the SS before matching (370)

* Signorovitch JE et al. Matching-Adjusted Indirect Comparisons: a new tool for timely comparative effectiveness research. Value in Health 15(2012) 940-947.

MAIC Example in Oncology – Unanchored - Results

MAIC Conclusions:

- Both the naïve and adjusted comparison suggested a superiority of treatment A compared to standard therapy B.
- MAIC adjustment improved the naïve comparison, mainly because patients had a less favorable OS prognosis in treatment A (IPD).
- MAIC can be performed in SAS, without using IML



A vs. B		
Comparison	Hazard Ratio [95%-CI]	p-Value
Naïve (before matching)	0.71 (0.57, 0.88)	0.001
Adjusted (after matching)	0.55 (0.40, 0.74)	<0.001

MAIC - Limitations

- Decision Population
  - MAIC gives estimates in the competitor population
  - Two sponsors will get different estimates from the same studies
- Treatment effect modifiers
  - May not be known
  - And/or information may not be in the published study
- Non-overlapping characteristics
- If comparing with older studies, study designs evolve, common comparators may no longer be so ‘common’
- Can’t use if endpoints or time-points differ – binary, continuous
  - For time-to-event outcomes, need data from digitized KM curve
- Difficult to use existing models to check fit, calibration of propensity score models
- Little overlap between population => low effective sample size (ESS)
- Matching across more baseline characteristics may mean more extreme weights

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THANK YOU

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BACKUP slides

MAIC Concepts and Theory – Unanchored ITC

- Without control arms, each trial corresponds to a unique treatment, and a patient can be characterized by the random quadruple (X, T, Y, C), where
  - X is a vector of baseline characteristics (e.g. age, sex, baseline disease severity, etc.),
  - T indicates the treatment received (e.g., T = 0 for pembrolizumab and T = 1 for atezolizumab),
  - Y is the outcome of interest (time to death or time to censoring)
  - C indicates if the patient died (C=0) or was censored (C=1). T.

- Observed data are based on realizations of the random quadruple (x_i, t_i, y_i, c_i) i = 1,…, n,
  - We observe the IPD (x_i, t_i, y_i, c_i) only when $t_i = 0$.
  - When $t_i = 1$, the IPD (x_i, t_i, y_i, c_i) are not observed individually, summary baseline characteristics (e.g., mean or median, proportion) and pseudo individual patient data are obtained from published Kaplan-Meier survival curves

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MAIC Concepts and Theory – Unanchored ITC

- In the context of OS analysis, given these observed data, the causal effect of treatment T = 0 vs. T = 1 on the outcome Y can be estimated as:

$$\text{Log[hazard]}_{T=0} \text{ (using estimated weights)} - \text{Log[hazard]}_{T=1} \quad (1)$$

  – where the weight used defined as $w_i = \frac{\Pr(T_i = 1|x_i)}{\Pr(T_i = 0|x_i)}$

  is the odds that patient i receives treatment T = 1 vs. T = 0 (i.e. enrolls in trial 1 vs. trial 0) given baseline characteristics x_i → patients receiving treatment T = 0 are re-weighted to match the distribution of receiving T = 1

- To apply this estimator, we must first estimate w_i for each patient with $t_i = 0$ from the observed data. As in matching methods based on propensity scores, the w_i may be assumed to follow the logistic regression model

$$w_i = \exp(\alpha + x_i'\beta) \quad (2)$$

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MAIC Concepts and Theory – Unanchored ITC

- Without IPD when ti = 1,
  - Maximum likelihood approach cannot estimate the parameters of this model.
  - Key feature of the proposed method is the use of a method of moments estimate for β in (2).
  - Inserting estimated weights based on the method of moments estimate into equation (1) gives the MAIC estimate

- Final estimate adjusts the patient population observed to receive treatment T = 0 by re-weighting each patient by the estimated odds of receiving treatment T = 1 vs. T = 0.
  - These weights exactly match mean baseline characteristics between treatments (or trials)

- This estimator can be obtained using SAS procedures (e.g., PROC PHREG)
  - With patient weights entered through the WEIGHT option.

- SEs for MAIC estimates are calculated using a robust sandwich estimator (Appendix of Signorovitch et al. [3]).
  - Sandwich estimators are derived empirically from the data
  - The robust sandwich estimator can be obtained through the use of COVSANDWICH option within PROC PHREG

MAIC Concepts and Theory – Anchored ITC

- With common control arms, data are incorporated by applying a standard adjusted indirect comparison [4] after first matching baseline characteristics across trials.
- The setting described in the above Section can be extended to observations of (*X, T, Z, Y, C*) where
  - *X, T, Y and C* are defined as in the above Section
  - *Z*=0 for the control arm and *Z*=1 for the treatment arm (treatment still depends on *T*, now thought as the trial indicator).
- IPD for (*X, T, Z, Y, C*) are observed only when *T*=0, however when *T*=1 we observe aggregate summary baseline (e.g., mean or median, proportion) and pseudo IPD are obtained from published KM survival curves for both arms:
  - $\bar{x}_1^{(0)}$ and $(y_1^{(0)}, c_1^{(0)})$ when Z=0 (i.e., control in trial T=1) and $\bar{x}_1^{(1)}$ and $(y_1^{(1)}, c_1^{(1)})$ when *Z*=1 (i.e., treatment in trial T=1).
  - The treatment effect (e.g., HR) and its 95% CI can also be observed (e.g. in the published literature).
- The estimate $\hat{\beta}$ can be obtained as described above by ignoring *Z*
  - pooled average baseline characteristics across trial arms may need to be computed from the aggregate data as $\bar{x}_1 = \frac{\left(\bar{x}_1^{(0)} n_1^{(0)} + \bar{x}_1^{(1)} n_1^{(1)}\right)}{n_1^{(0)} + n_1^{(1)}}$, where $n_1^{(0)}$ and $n_1^{(1)}$ are the numbers of patients in trial *T*=1 with *Z*=0 and *Z*=1)
- The estimated treatment effect, based on a matching-adjusted indirect comparison, is then calculated as before

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