Comparison of Novel Multilevel-Network Meta-Regression With Other Conventional Indirect Treatment Comparisons

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Background

- When direct head-to-head trials between treatments of interest are not available, indirect treatment comparison (ITC) methods such as matching-adjusted indirect comparison (MAIC), Bayesian network meta-analysis (BNMA) allows researchers to estimate the relative effects of two treatments using fixed effects model (FEM) and random effects model (REM).
- MAIC is covariate- adjustment based ITC that relies on propensity score weighting technique to report effective sample size (ESS) and is said to have imperfect precision in case of small ESS.[1]
- Two-stage MAIC (2SMAIC)[1] is an extended approach to counter some of the limitations of standard MAIC as it allows for comparisons beyond just two treatments, potentially including multiple treatments in a network
- Analyses within BNMA framework involve data, a likelihood distribution, a model with parameters, and prior distributions for these parameters.
- Recent developments shows that multilevel network meta-regression (ML-NMR) developed by Philippo et.al., 2020[2] is becoming increasingly important as it extends the capabilities of standard ITCs
- Motivation of this study is to understand and adopt a versatile method to perform ITCs. Thus, it becomes increasingly important to highlight the differences among all the key ITC approaches.
- While ML-NMR addresses some methodological challenges, it is important to evaluate how it fares against other conventional ITC approaches
- As the differences in effect modifiers between studies can affect BNMA results, ML-NMR uses common regression coefficients, a blend of individual patient data (IPD) as well as study-level aggregate data over a network of evidence to report relative treatment effects.
- ML-NMR also allows the extrapolation of results based on the set of covariates relevant to any decision problem

Methods

- VIRTUAL is simulated individual patient-level data (IPD) with covariate values generated at the patient level using the Wakefield package in R, and NewTech is a hypothetical treatment.
- The analysis included three studies reporting data on metastatic castration-resistant prostate cancer, with one study (VIRTUAL) reporting IPD for 356 subjects (224 on NewTech and 132 on Androgen Receptor Pathway Inhibition (ARPi)).
- Two other studies reported aggregate level data, CARD[3] (Cabazitaxel vs ARPi) and PROfound[4] (Olaparib vs ARPi) (See **Fig 1**).
- Our descriptive analysis included mean age at baseline, proportion of subjects with Eastern Cooperative Oncology Group (ECOG) score of 0 and 1, mean prostate specific antigen (PSA) level at baseline, and proportion of PSA responders (see **Table 1**).
- **Standard MAIC** involves a logistic propensity score model that is conditional on baseline covariates. This is equivalent to the following model on the dependent variable of log weight as given in NICE TSD 18.[5]

$$log(w_i) = \alpha_0 + \alpha_1^T X_i$$

where α is a vector of covariates that predict weight, and X_i^{EM} is the patient characteristic.

- **2SMAIC** extends the standard MAIC approach and considers balancing treatment arms of index trial given by:

$$log(Prob(T = 1|X_i) = \beta_0 + \beta_1^T X_i$$

meaning conditional probability that a subject will be assigned to treatment 1 based on observed covariates X_i.

- Using 2SMAIC, the weights from the standard MAIC are further rescaled by the estimated treatment weights to obtain final weights of each subject and in the process effective sample size (ESS) is estimated.
- **BNMA** based on fixed effects model for PSA response is based on a binomial likelihood with a log link function.
  - The results of the BNMA are based on 200,000 iterations on three chains, with a burn-in of 50,000 iterations. Convergence was assessed by visual inspection of trace plots.
- **ML-NMR** results in less biased estimates when compared to conventional NMA without covariates.[6]
  - ML-NMR relies on a two-step approach where the first step involves defining a regression model at the IPD level followed by integrating it over aggregate level data (AgD).
  - IPD level model for the binary outcome of success or failure to achieve PSA response is defined as:

$$y_{ijk} \sim Bern\,(pijk\,)\ \textit{(Bernoulli distribution)};\ \ p_{ijk} = \theta_{ijk} = \varphi\,\{\mu_j + \boldsymbol{x}^T_{ijk}(\beta_1 + \beta_{2\_k}) + \delta_k\}$$

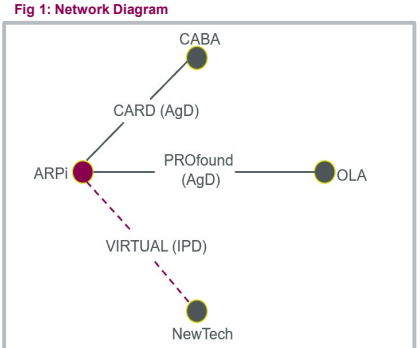
Whereas the aggregate level model which is based on total number of responses is obtained by integrating individual Bernoulli outcomes given by:

$$y_{\cdot\_jk} \sim Bin\,(Njk, \overline{p_{jk}})\ \textit{(Binomial distribution)};\ \overline{p_{jk}} = \theta_{\cdot\_jk} = \int \varphi\,\{\eta_{jk}(x)\}\, f_{jk}\,(x)\,dx;\ \eta_{jk}(x) = \mu_j + \boldsymbol{x}^T_{ijk}(\beta_1 + \beta_{2\_k}) + \delta_k$$

where y_{ijk} and p_{ijk} denotes the likelihood of PSA response and the probability of success of PSA response; μ_j represent study-specific baselines, β_1 and $\beta_{2,k}$ represent the mean effect of covariates and treatment specific effect modifiers, in case if it is known that a particular covariate is not prognostic or effect modifying respectively, subsequently the coefficients in β_1 and $\beta_{2,k}$ can be set to 0, lastly δ_k is the treatment effect of the k[th] treatment relative to the reference.[2]

- ML-NMR results for fixed effects model under the Bayesian framework were based on 100,000 iterations on four chains with 20,000 warm up values for each chain.

Fig 1: Network Diagram



AgD: aggregate data; IPD: individual patient data; VIRTUAL: simulated trial; CABA: cabazitaxel; OLA: olaparib; NewTech: hypothetical intervention

Results

- All four ITC's showed NewTech is statistically significantly better than ARPi.
- Conventional BNMA using FEM and REM reported similar relative effect estimates between NewTech and ARPi.
- By default, ML-NMR presents the results based on the weighted mean of all covariates reported in the regression model. This includes all the studies in the analysis, NewTech vs ARPi (OR: 95% CrI: 5.87 (3-12.8). (See **Table 2**)
- Additionally, we obtained relative effect estimates between NewTech vs ARPi using weighted mean of age, proportion having ECOG [0,1], and PSA level based on VIRTUAL trial.
- The results from ML-NMR based on a VIRTUAL trial were consistent with BNMA results and provided a conservative point estimate in favor of NewTech.
- Comparison of ML-NMR results with BNMA showed insignificant differences and can be concluded that no additional impact of baseline covariates could be seen.
- Both standard and 2SMAIC estimated higher odds of response with NewTech when compared to ARPi.

Table 1: Mean value of covariates in included studies

Trial (Interventions)		N	Mean value of covariates		
			Age, mean (SD)	Proportion ECOG [0,1]	PSA level, mean (SD)
VIRTUAL	NewTech	224	70 (7.45)	0.96	328.6 (253.8)
	ARPi	132	70.3 (7.71)	0.95	344.6 (244.1)
CARD	Cabazitaxel	129	70 (9.75)	0.95	264.4 (1352.5)
	ARPi	126	71 (10.75)	0.94	232.9 (453.8)
PROfound	Olaparib	162	68 (9.75)	0.93	62.2 (65.9)
	ARPi	83	67 (9.25)	0.96	112.9 (72.1)

Table 2: Results based on all ITCs

Comparison	Indirect Treatment Comparison Results					
	ML-NMR (OR: 95%CrI)		BNMA (OR: 95%CrI)		Standard MAIC (OR: 95%CI)	2SMAIC (OR: 95%CI)
	Weighted*	^VIRTUAL	FEM	REM		
NewTech vs ARPi	5.87 (3-12.8)	4.81 (2.7- 9.12)	4.32 (2.5- 7.51)	4.35 (1.35-14.32)	9.83 (2.69- 35.98)	11.64 (3.12- 43.48)

*Based on weighted mean from VIRTUAL, CARD, and PROfound trials; ^based on IPD from VIRTUAL trial; ML-NMR: Multilevel-Network meta-regression; FEM: Fixed effects model; REM: Random effects model; BNMA: Bayesian network meta-analysis; OR: Odds ratio; CrI: Credible interval; CI: Confidence interval; MAIC: Matching adjusted indirect comparison: 2S: Two-stage

Conclusions

- Conventional BNMA is more effective and provides reliable estimates in cases where the study and patient characteristics have significant overlap across the studies.
- Both FEM and REM results were similar and showed efficacy benefit for NewTech vs ARPi.
- Standard MAIC is useful in cases where there is disjoint network or even if there is single comparator, whereas for 2SMAIC, an anchored comparison is required.
- 2SMAIC has additional benefit over standard MAIC as it also takes into account the allocation of treatment based on particular value of a covariate.
- Both MAIC and 2SMAIC presented similar results with 2SMAIC showing slightly higher benefit in favor of NewTech.
- ML-NMR additionally adjusted for mean age at baseline, proportion of subjects with ECOG score of 0 and 1, mean PSA level at baseline and proportion of PSA responder.
- Results based on overall weighted mean showed slightly higher odds of response in favor of NewTech when compared to conventional BNMA.
- Extrapolated results based on VIRTUAL trial provided a conservative estimate of odds ratio in favor of NewTech when compared to overall result.
- Our findings indicate that the conventional BNMA, MAIC, 2SMAIC and ML-NMR generated similar results with ML-NMR depicting a more promising assessment of PSA response by incorporating baseline characteristics and providing an opportunity to overcome the conventional ITC limitations.

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