ISPOR Europe 2023

12 - 15 November

Poster Tour Guide Packet

Poster Session:	**Poster Session 2**
Tour Name:	**Methodology Research in HEOR**
Tour Date/Time:	Monday, 13 November 2023 | 15:30 - 16:15
Tour Location:	Area A, Poster and Exhibit Hall, Hall C

Acceptance Code:	PT13
Board Number:	1A
Abstract Title:	An Evaluation of the Impact of Evidence Grouping on Certainty Rating When Performing a Grade Assessment Without a Meta-Analysis
Presenting Author:	Lucia Giles

Abstract Body:

OBJECTIVES: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) provides a reproducible, transparent framework for rating the certainty of a body of evidence identified systematically. Meta-analysis is often used to inform GRADE assessment but may not always be feasible, especially where the evidence is heterogenous. We analyzed the impact of evidence grouping on certainty rating as per the GRADE framework in the absence of a meta-analysis.

METHODS: We applied the GRADE framework to systematically identified randomized controlled trials (RCTs) comparing the patient-important outcome, rate of annual exacerbations (moderate or severe), in patients with chronic obstructive pulmonary disease (COPD) following triple or dual therapy. One assessment considered all evidence identified on the endpoint of interest, whereas another split evidence by measurement criteria; the evidence certainty rating was compared between assessments.

RESULTS: Five RCTs were identified that reported on rate of annual COPD exacerbations; all studies reported a statistically significant lower annual rate of exacerbations with triple vs dual therapy. When all identified evidence was assessed as a single group, the certainty of evidence was rated “very low”. However, when the evidence was grouped by measurement criteria, the three outcomes measured using the same criteria had a “moderate” certainty rating. The two remaining outcomes, in which the measurement criteria were not reported, were rated as “very low” certainty owing to downgrading in the indirectness and imprecision domains (non-reporting of outcome measurement methodology), differences in follow-up periods and lack of reporting on statistical power.

CONCLUSIONS: We illustrate how evidence grouping can affect certainty ratings as per the GRADE framework, and highlight the need for careful consideration of potentially confounding factors even in the absence of meta-analysis. This is especially pertinent when considering the growing body of literature including real-world evidence and the inevitable source of heterogeneity associated with different study designs.

Tour Guide’s Questions for Starting Q&A (Each poster will have ~5 minutes for Q&A with attendees/Tour Guide)

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Acceptance Code:	PT14
Board Number:	2A
Abstract Title:	Bayesian Meta-Analysis of Data From Trials of Mixed Patient Populations to Inform Health Economic Models for Patients Harboring a Predictive Biomarker
Presenting Author:	Lorna Wheaton

Abstract Body:

OBJECTIVES: Genetic biomarkers are investigated in trials with mixed populations to identify subsets of a population who might benefit from targeted therapies. Mixed populations introduce complexity when combining trials in meta-analysis, particularly when subgroup analyses are not conducted or reported. Data from such trials are typically discarded, thus methods for more efficient use of all relevant data are required.

METHODS: We propose Bayesian random-effects meta-analysis, assuming a systematic difference in treatment effects between biomarker subgroups, to efficiently combine aggregate data from all relevant trials to obtain accurate and precise treatment effect estimates for a biomarker subgroup of interest. Pooled treatment effects are included in a probabilistic partitioned survival model to estimate incremental cost-effectiveness ratios (ICERs).

RESULTS: The method was applied to colorectal cancer trials reporting analysis of wild-type (WT), mutant-type (MT) and Mixed (WT+MT) KRAS biomarker groups. Using WT subgroup data alone resulted in hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) of 0.79 (95% credible interval [CrI]: 0.69, 0.90) and 0.90 (95% CrI: 0.75, 1.06). Addition of MT and Mixed data resulted in HRs for PFS and OS of 0.79 (95% CrI: 0.70, 0.87) and 0.90 (95% CrI: 0.81, 1.00), thus improving precision of estimation of the HRs by 19% and 40% respectively. Using data from WT, MT, and Mixed subgroups in the health economic model reduced the CrI width around the ICER estimate by 20% compared to using data from WT subgroup analysis only.

CONCLUSIONS: The proposed method for synthesising all available trial data with partially reported subgroup analysis reduces uncertainty around pooled treatment effect estimates for biomarker subgroups compared to meta-analysis of a reduced set of trials reporting treatment effects on a specific biomarker subgroup. Furthermore, more precise effectiveness estimates obtained from meta-analysis result in improved estimates of uncertainty around the ICER for the biomarker subgroup.

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Acceptance Code:	PT15
Board Number:	3A
Abstract Title:	Comparing the Impact of Random Forest Vs Bayesian G-Computation on Matching-Adjusted Indirect Comparisons of Treatments Between Trials: A Simulation Study
Presenting Author:	Gabriel Tremblay

Abstract Body:

OBJECTIVES: Matching-adjusted indirect comparison (MAIC) is a common method of population-adjusted indirect treatment comparison between two studies. It uses a propensity score (PS) weighting approach which is sensitive to poor effect modifier (EM) overlap and small sample size of the index trial as reweighting often leads to significantly smaller effective sample sizes. G-computation is a marginalization method that can achieve more accurate estimates than MAIC when EM overlap is poor. Random forest (RF) is a non-parametric ensemble technique that averages outcomes from multiple decision trees and can weight patient characteristics based how many times any pair of subjects ends up in the same terminal nodes. This study aimed to evaluate and compare the convergence and fitting of RF and G-computation in sample sizes <100.

METHODS: Data were simulated for an anchored two-study comparison (AB and AC) with three treatment levels. The MAIC included five covariates: two EMs (age, time since diagnosis) and three prognostic variables (smoking status, race, sex). Weights were estimated to match the between-trial EM distributions. MAICs using RF, G-computation, and PS approaches were applied over 1,000 iterations.

RESULTS: MAIC with RF converged in all iterations (sample size = 50), while MAICs with PS and G-computation converged in zero and 34 out of 1,000 iterations, respectively. Mean absolute error (MAE, i.e., absolute difference between the point estimates of the log odds ratio of treatment C vs B) was significantly lower using the RF approach and their true value averaged over the converging G-computation iterations (MAE=0.94 vs. 1.42, p<0.001).

CONCLUSIONS: This simulated study demonstrated that RF was an alternative, highly accurate MAIC method when there is a small sample size and poor imbalance. Additional simulation and patient-level data studies should be conducted to explore results with varied sample sizes, sparse data, and number of covariates.

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Acceptance Code:	PT16
Board Number:	4A
Abstract Title:	Impact of Data Maturity on the Estimation of the within-Trial Hazard Function: An Example from Metastatic Castration Resistant Prostate Cancer
Presenting Author:	Jack Williams

Abstract Body:

OBJECTIVES: Cost-effectiveness analyses often use parametric survival models fitted to clinical trial data to predict lifetime outcomes. Guidelines recommend that empirical (observed) and modelled hazard functions are presented to assess model fit and the plausibility of extrapolated hazards. The accurate estimation of the empirical hazard function is critical to making an informed choice of extrapolation. We compare different methods of estimating the empirical hazard and assess whether these methods consistently estimate the hazard function across three reported analyses of a prostate cancer study (NCT01212991).

METHODS: Pseudo-patient level data were recovered from published Kaplan-Meier plots for enzalutamide. Hazards for overall survival were estimated at data cut-offs (DCOs) with 34-, 44- and 81-months maximum follow-up. Unsmoothed hazards were estimated using the muhaz R package (pehaz function) and smoothed hazards were estimated using the muhaz and bshazard packages. The shapes of different hazard functions were compared to understand how these differed by estimation method and data availability.

RESULTS: At longest follow-up (DCO3), the empirical hazards initially increased (0-20 months), before remaining broadly constant thereafter, with muhaz and bshazard estimating similar smoothed functions. The empirical and smoothed hazards at earlier DCOs were generally consistent with DCO3 up to approximately 30 months (~4% at risk, DCO1). After month 30, muhaz estimated increasing (DCO1) and then decreasing (DCO2) hazards whilst bshazard estimated decreasing (DCO1) and constant (DCO2) hazards, respectively. In this example, bshazard provided smoother hazard functions than muhaz and was less sensitive to changes in the hazard at the tail.

CONCLUSIONS: In this study, the empirical hazard function appeared generally robust to the choice of smoothing function until numbers at risk were small. The hazard trend at the tail of the curve can differ considerably depending on function used. Where uncertain, the clinical plausibility of the empirical hazard function should also be considered when informing extrapolation.

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Acceptance Code:	PT17
Board Number:	5A
Abstract Title:	Modelling Treatment Duration in Psoriasis: Examining Extrapolation Approaches and Implications
Presenting Author:	Henri Leleu

Abstract Body:

OBJECTIVES: Modeling treatment duration (TD) is crucial for cost-effectiveness and budget impact analyses in chronic diseases. Markov models assume constant treatment interruption risks, implying that all patients eventually drop out of treatment, which may not be realistic. We examined TD extrapolation approaches for moderate to severe psoriasis (MSP) and proposed a decision framework.

METHODS: Exponential distributions were fitted to real-world TD data to model TD for biotherapies in French MSP patients. Although median TD was short (1.5 years), 12-year follow-up available for Infliximab showed a plateau with 6.7% of patients still on treatment after 10 years. Thus, a plateau parameter was introduced to cap the discontinuation rate. This raised the question of the magnitude of the plateau for other biotherapies. We tested two potential approaches and compared their impact on the modelled TD for Infliximab and Interleukine(IL)-23: 1) plateau is treatment-response-dependent and response HR were applied to the plateau to estimate plateaus' levels for IL-23; 2) plateau is patient- or practitioner-dependent with a similar level across treatments.

RESULTS: Modelling without accounting for the plateau yielded median TD of 1,4 years for Infliximab, with <1% patients on treatment at 10 years. Accounting for the plateau led to accurate TD (median = 1.5 years, 6.9%/6.2% on treatment at 10/20 years). Not accounting for TD plateau, modelled IL-23 median TD was 3.68 years and 15%/2.3% of patients were on treatment at 10/20 years. Approaches 1 and 2 respectively increased median TD (%patients treated at 10/20 years) of +0.8 (27%/16%) and +0.4 years (21%/8%).

CONCLUSIONS: Accurate extrapolation of TD with Markov models may require adaptations to avoid underestimating TD, likely to bias cost-effectiveness or budget impact results. Addressing this issue raises the question of the determinants of treatment-maintenance that should be addressed through face validation of model estimates, expert opinion, or biological plausibility.

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Acceptance Code:	PT18
Board Number:	6A
Abstract Title:	Novel Approaches to Unify Multi-State Transition Modelling Methods and Develop a Synthetic English Population to Support Health Economic Evaluation Studies
Presenting Author:	Jamie Kettle

Abstract Body:

OBJECTIVES: General population health transition data are frequently unavailable in a suitable format to support evaluation studies, including cost-effectiveness, health policy and intervention modelling. We aimed to: (1) develop a representative synthetic English population capturing health status at small area level, and (2) apply three key multi-state transition modelling methods for estimating life expectancies (LEs) and healthy life expectancies (HLEs): the Sullivan life table method, continuous-time and discrete-time Markov models.

METHODS: Gompertz distributions were fitted to 2017-2019 age-specific health status and mortality data from the Office for National Statistics (ONS) to generate a synthetic population. A continuous-time multi-state model was fitted to the data to estimate HLEs and LEs. Finally, discrete-time transition probabilities estimated from the continuous-time model were used to create an Excel-based Markov model, providing an alternative method of estimating HLEs and LEs. All estimates were compared with HLEs and LEs at English local authority level in 2017-2019, estimated by the ONS using the Sullivan method.

RESULTS: The different methods tested replicated ONS estimates well: • The synthetic population showed similar distributions of ages at illness and death as ONS-reported estimates.

• Differences in mean HLEs and LEs (synthetic population vs ONS-estimated) were small (HLEs: -0.1% for men, 1.8% for women; LEs: 0.1% and 0.3%), and differences for most local authorities were smaller than +/-10%.

• Differences for the discrete- vs continuous-time HLEs and LEs were also similar (-0.7–0.7%).

CONCLUSIONS: We have generated a synthetic general population at England local area level suitable for use in evaluation studies, adopting an approach which could equally be applied to populations with chronic diseases or to other countries. The continuous-time and discrete-time Markov models fitted to the synthetic population both replicated ONS Sullivan life table method estimates of HLEs and LEs well, offering flexibility for researchers.

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