

Statistical Training for Health Technology Assessment Statistical Programmers

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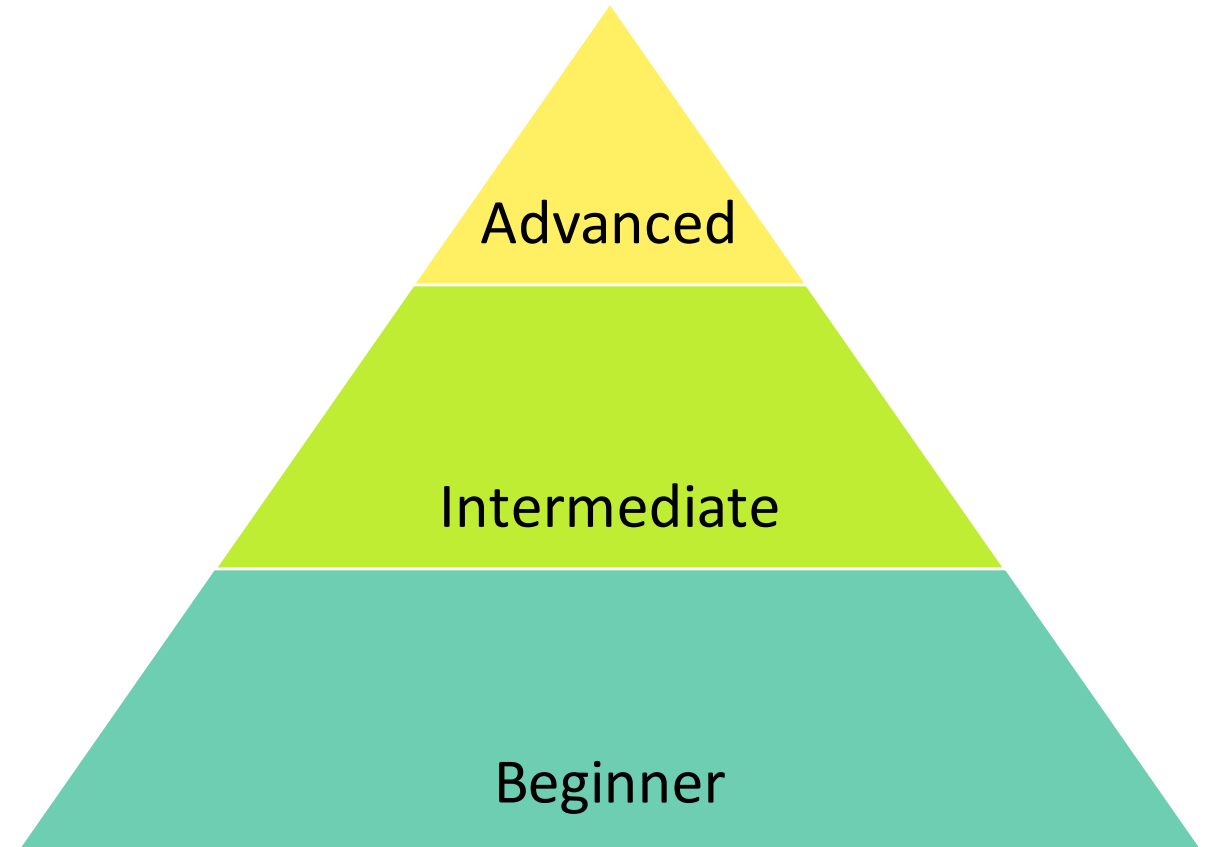


Agenda

1. Introduction
2. Collaboration Between Statistics and Statistical Programmers
3. Training Preparation
4. Training Implementation
5. Training Content
6. Conclusion

Introduction

- Health Technology Assessment (HTA) dossier may include statistical analyses varying from simple summaries of clinical trial results to implementation of more complex statistical methods.
- The statistical programming team is a fast-growing team. The number of employees grew substantially in recent years to address the growing HTA business needs.
- The SP team works in partnership with a team of HTA statisticians, a good statistics culture is important for optimal collaboration with statisticians.
- In 2020, the initiative 'Statistical Training for Statistical Programmers in HTA' has been launched.



Collaboration between Statisticians and Statistical Programmers in HTA

Statisticians & Statistical Programmers in HTA

- Our offices are located in London, Brussels and Zürich.
- The team provides analytical and programming expertise.
- We use clinical data to analyze the efficacy and safety profile of our compounds.
- We create HTA dossiers using scientific concepts, statistical analysis and high-quality data.
- Complexity of the statistical methodology in HTA dossiers increases.
- Each HTA report is the fruit of cross functional collaborations.

Training Goals

- Give all statistical programmers a good understanding of HTA-specific statistical methods.
- Improve the collaboration between statisticians and statistical programmers.
- Better understanding of the specifications provided by the statisticians.
- Better QC of the deliverables by programmers.
- Job satisfaction of both functions.



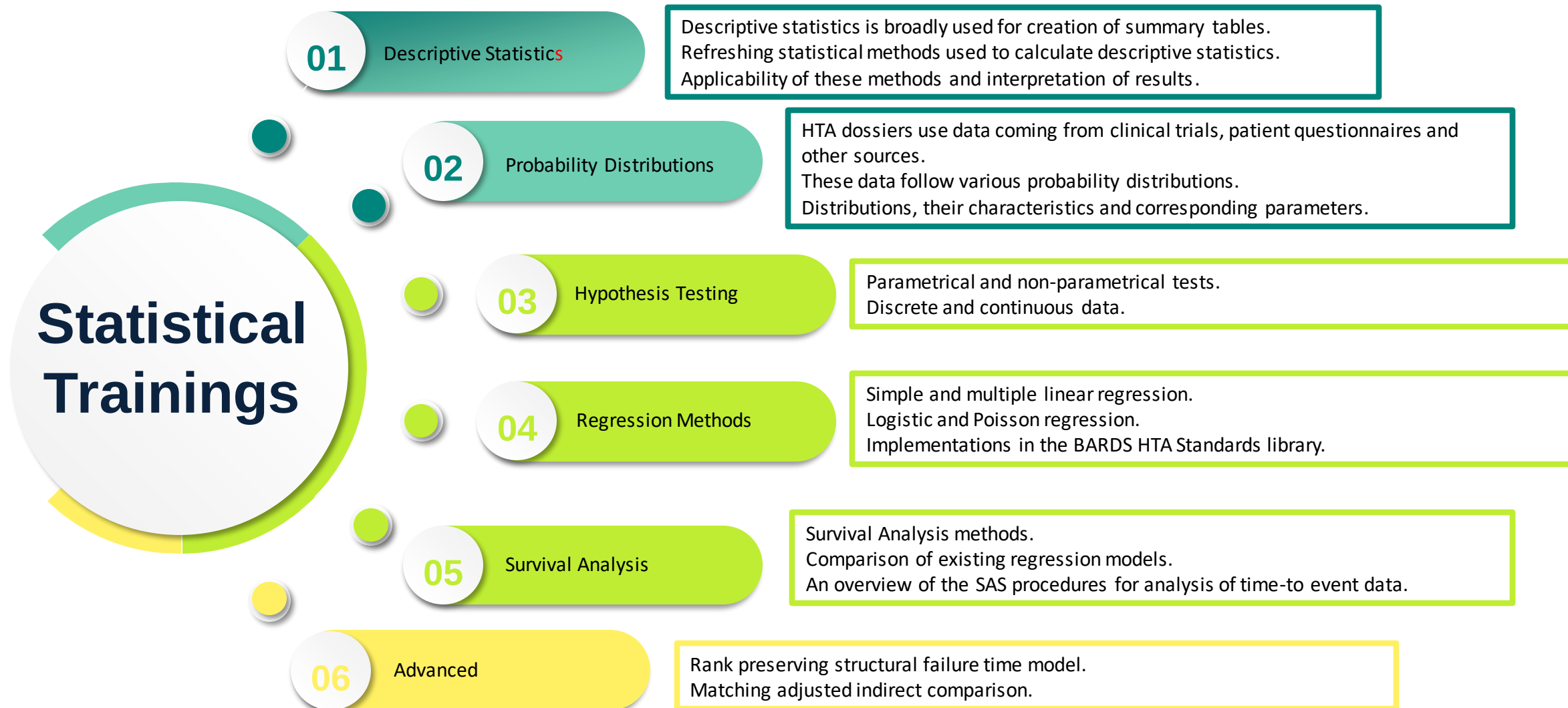
Training Preparation

Statistical concepts for HTA Statistical Programmers

Training Plan

Modules	Title	Trainer	Unmet need identified by Statistical Programmers staff
Beginner	Descriptive Statistics	HTA SP	20%
	Probability Distributions	HTA SP	20%
Intermediate	Hypothesis Testing	HTA SP	40%
	Regression Methods	HTA SP	60%
	Survival Analysis	HTA Statistician	20%
Advanced (HTA specific)	Rank-Preserving Structural Failure Time model	HTA Statistician	60%-100%
	Matching Adjusted Indirect Comparisons	HTA Statistician	60%-100%

Training Content



Survival Analysis

The main goal is to analyze the duration between a start time and the time of occurrence of an event (positive or negative)

Survival analysis (more generally, time-to-event analysis) is a critical methodological approach in drug development and, specifically HTA

- Events matter to patients (concept of patient relevant outcome in HTA)
- Events are very important in a public health decision framework (a treatment effect on a marker may not imply an effect on the important event endpoint)
- Events are typically associated with high healthcare costs and important consequences
- Survival analysis looks at risk of the occurrence of the event and when it occurs

Disease	Marker	Event
Hypercholesterolemia	LDL-Cholesterol	Cardiovascular death, stroke
Hypertension	Blood pressure	Cardiovascular event
Osteoporosis	Bone mineral density	Vertebral fracture
Oncology	Response to treatment	Death

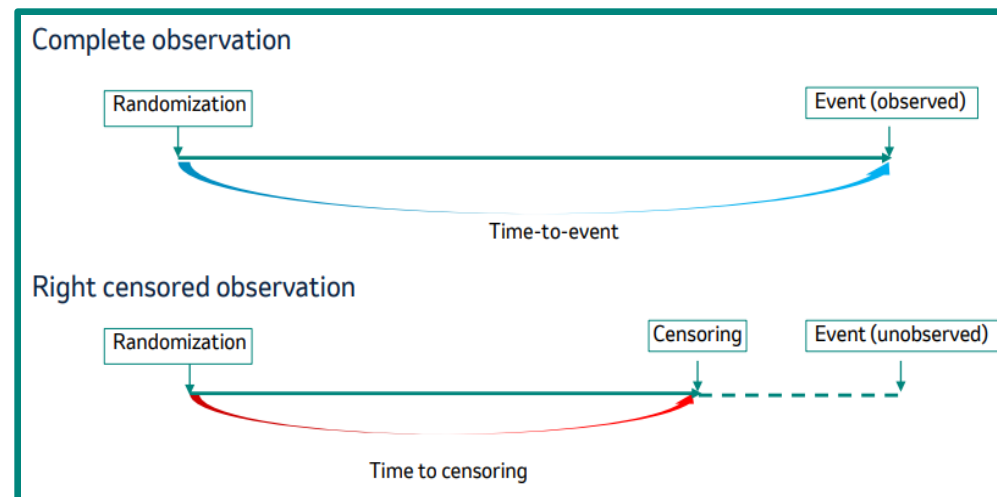
Survival Analysis

Time-to-event data cannot be analyzed using standard statistical techniques for experimental designs (such as t-test, analysis of variance or logistic regression)

1. Time-to-event data are typically incomplete

- We cannot wait until every participant has experienced an event before to analyze the study. There is a censoring process.
- Ignoring the censoring and applying standard methods for complete data will provide biased estimates and incorrect statistical tests.

2. Time-to-event random variables take positive values and their statistical distribution is typically not (approximatively) normal. In life sciences, no parametric distribution has a central role.



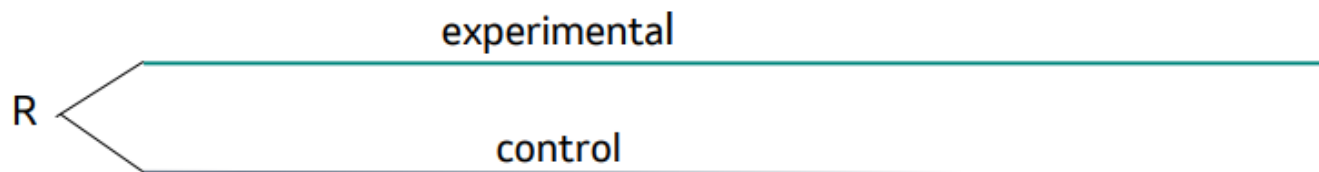
➔ Need for specific statistical methods:

- Descriptive statistics (Kaplan-Meier estimate of time-to-event curve)
- Non-parametric testing (Log-Rank)
- Semi-parametric modelling (Cox regression)
- Parametric regression, when appropriate

Rank Preserving Structural Failure Time Model

Problem statement

Treatment switching commonly occurs in oncology trials.



Some control patients switch from the control treatment to the experimental treatment after progression of disease (**PD**).



The treatment switch causes bias in analyses for endpoints measured after treatment switch.

- Outcome in control arm reflects partially the effect of the experimental drug.
- Treatment switch is a selective process (not all patients who progress in the control arm switch).
- Timing of treatment switch varies.

Rank Preserving Structural Failure Time Model

Concept

Goal: estimate what the treatment effect (experimental relative to control) would have been if switching had not occurred (hypothetical strategy estimand)

Why: The estimation of the treatment effect after adjustment for switching is important in HTA filings: in economic modeling, to compare the new treatment status with the status without the new treatment

Idea:

- Each patient proceeds through disease process towards his/her death at his/her own speed.
- An experimental therapy slows this speed down by a certain multiplying factor.
- This factor is assumed to be the same for the patients regardless of the treatment arm they were initially randomized to, and regardless of whether experimental therapy is given from the time of randomization or from the time of treatment switching.
- The Rank Preserving Structural Failure Time Model (RPSFT) applies this slow-down factor to patients who switched, to estimate event times that would have been observed had these patients not switched to the experimental treatment.

Rank Preserving Structural Failure Time Model

%rpsft macro

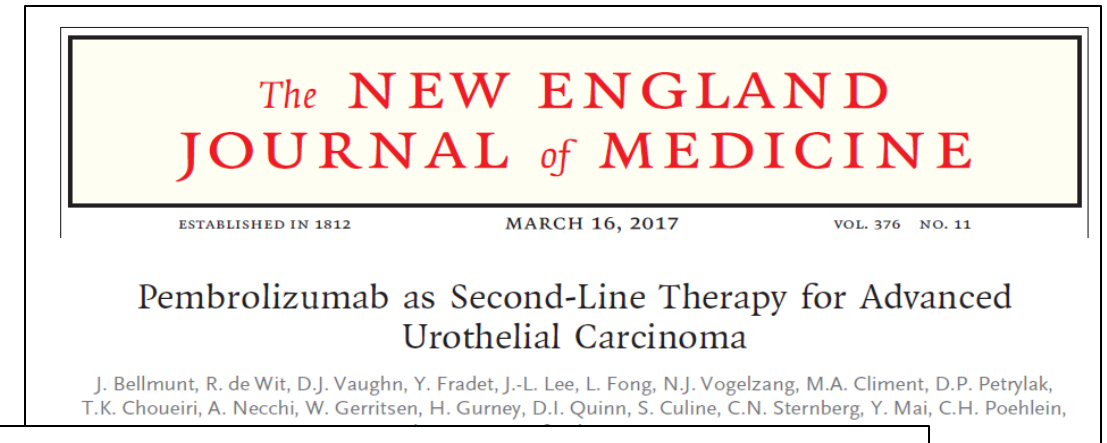
- Developed in 2020 by the programming and statistical HTA teams.
- SAS tool to create RPSFT statistics, datasets, tables and plots.
- Designed to be used in SAS 9.4.
- Robust and covers different analysis situations.
- The macro flexibly controls the output tables and plot appearance.
- Interpretation of macro outputs is an essential part of quality control at the development stage of HTA deliverables.

User manual

- Macro overview.
- Basic features.
- Macro syntax.
- Statistical method used for calculations.
- Detailed examples.
- Frequently asked questions.

Matching Adjusted Indirect Comparison

- Results of randomized clinical trials are the standard foundation for evidence-based clinical guidelines and reimbursement decisions.
- In the presence of multiple approved treatment options, comparison of all relevant treatments may be required for clinical and reimbursement decision making.
- Randomized clinical trials directly comparing all available treatments head-to-head would in some ways be an ideal solution but such evidence is unlikely to exist.
- A new treatment may need to be compared to placebo, standard of care or a competitor treatment.



Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial



Thomas Powles, Ignacio Durán, Michiel S van der Heijden, Yohann Loriot, Nicholas J Vogelzang, Ugo De Giorgi, Stéphane Oudard, Margitta M Retz, Daniel Castellano, Aristotelis Bamias, Aude Fléchon, Gwenaëlle Gravis, Syed Hussain, Toshimi Takano, Ning Leng, Edward E Kadel III, Romain Banchereau, Priti S Hegde, Sanjeev Mariathasan, Na Cui, Xiaodong Shen, Christina L Derleth, Marjorie C Green, Alain Ravaud

Matching Adjusted Indirect Comparison

Comparator Study



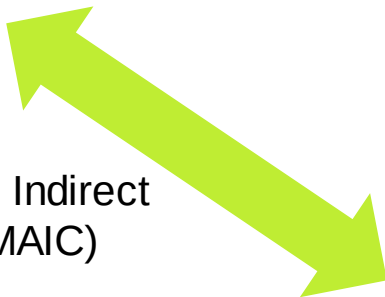
In-House Study



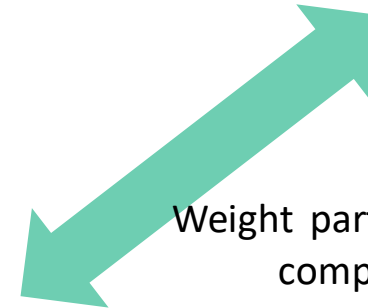
Different Characteristics



Matching Adjusted Indirect
Comparisons (MAIC)

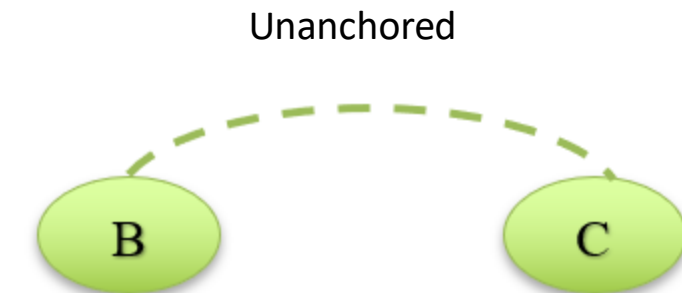
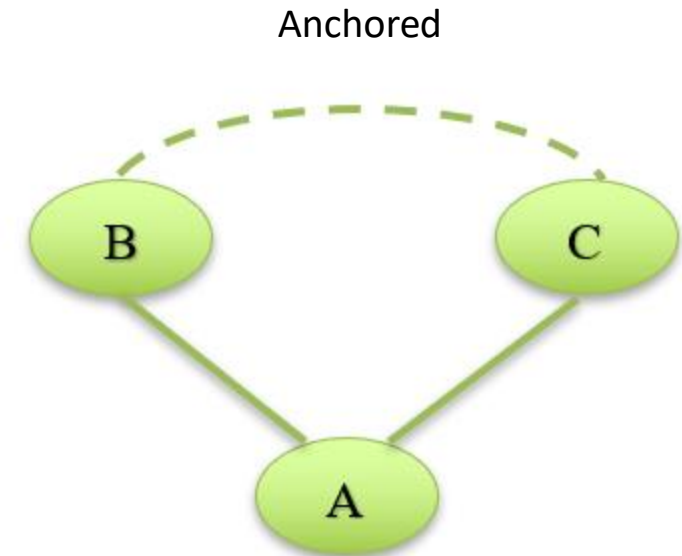


Weight participants to match
competitor study



Matching Adjusted Indirect Comparison

- Within randomized clinical trials, results are not biased due to the randomization.
- Comparing results for treatment B in trial AB with results for treatment C in trial AC is prone to bias, as responses for common treatment arm A may differ across studies. Sources of cross-trial differences include design, conduct, populations and characteristics
- MAICs were developed to address these issues.
- Relevant, pre-defined baseline characteristics are selected and an algorithm is used to define unique weights for all participants in the sponsor trial.
- The method was developed with the knowledge that individual patient data (IPD) is rarely available for both trials. More often a researcher has access to IPD only for one study.
- For the comparator treatment, only published summary data is usually available. MAICs can combine IPD from the experimental study with published summary results for other treatments of interest.



Conclusion

- Training in innovative and HTA specific methodologies is new in the industry.
- Training implementation is resource consuming.
- Level of understanding of methods and approaches realized in HTA dossier is increased.
- 30% to 70% of the team depending on the module were trained.
- Training sessions are useful and meets the goals. A second edition is planned.
- New trainings in the overall survival analysis adjusted for switchover and patient reported outcome analysis will be proposed.



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References

Halmos, B, Burke, T, Kalyvas, C, Insinga, R, Vandormael, K, Frederickson, A, Piperdi, B. Matching-Adjusted Indirect Comparison of Pembrolizumab + Chemotherapy vs. Nivolumab + Ipilimumab as First-Line Therapies in Patients with PD-L1 TPS $\geq 1\%$ Metastatic NSCLC. *Cancers*, 12(12), 3648. 2020.

Halmos B, Burke T, Kalyvas C, Vandormael K, Frederickson A, Piperdi B. Pembrolizumab+chemotherapy versus atezolizumab+chemotherapy+/-bevacizumab for the first-line treatment of non-squamous NSCLC: A matching-adjusted indirect comparison. *Lung Cancer*. 2021 May;155:175-182.

Coppin, F, Kampouris, H, Cao, Y. (2020) Managing an International Statistical Programming Team in the Era of New Ways of Working. Proceeding of PhUSE EU Connect 2020.

Guide to Understanding Health Technology Assessment (HTA). Institute for clinical and economic review. 2018

Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, Lee K, Boersma C, Annemans L, Cappelleri JC. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health*. 2011 Jun;14(4):417-28.

Massaad R, Malbecq W, Kampouris H, Gelb D. Matching-Adjusted Indirect Comparison (MAIC) in HTA and its application using SAS Procedures. PhUSE Single Day Events. 21st September. 2018.

Nutzenbewertungsverfahren zum Wirkstoff Pembrolizumab (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, Nicht-Plattenepithelhistologie, Erstlinie, Kombination mit Pemetrexed und Platin-Chemotherapie). 2019 https://www.g-ba.de/downloads/92-975-3022/2019-03-29_Modul4B_Pembrolizumab.pdf

Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Vandormael K, Riccio A, Yang J, Pietanza MC, Brahmer JR. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. *J Clin Oncol*. 37(7):537-546. Mar 1, 2019

Robins JM, Tsiatis AA: Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Stat Theory Methods*. 20:2609-2631, 1991

Saag K, Petersen J, Brandi ML, Karaplis A, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A. A Randomized Alendronate-Controlled Trial of Romosozumab: Results of the Phase 3 Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk. *Arthritis Rheumatol*. 2017; 69

Signorovitch et al, Matching-Adjusted Indirect Comparisons: A New Tool for Timely Comparative Effectiveness Research, *Value in Health* 15, 940-947. 2012