Invited Sessions | Wednesday 30 August 2023

WIN1.2 Estimating the marginal and conditional means of recurrent events in presence of terminal events

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In many clinical and epidemiological studies, to assess disease progression over time, it is of great interest to study recurrent events, i.e., the repeated occurrence of the same event over time, when a terminal event may also be experienced. This problem is particularly relevant in practice when the rate of the terminal event is high. A very relevant measure for studying disease progression is the marginal mean of the number of recurrent events, experienced prior to the terminal event. Its functional form can be studied over time and compared for different covariate levels. Another interesting key measure is the conditional mean number of recurrent events for the survivors of the terminal event, and for those who have died before a specific time. First, we present a class of efficient IPCW estimators based on a dynamic prediction augmentation (dynamic AIPCW estimators), derived using semi-parametric efficient estimation theory for right- censored data. We discuss the amount of efficiency gain provided by these estimators and show that standard estimators are efficient in settings with no heterogeneity, but, in other settings with different sources of heterogeneity, the efficiency can be greatly improved when dynamic AIPCW are employed, at no extra cost to robustness. Moreover, we show that various regression models can be used to assess the impact of covariates in reducing or increasing the mean number of recurrent events. When a terminal event is present, the same covariates may affect simultaneously the recurrent and terminal events, and play a different role for survivors and for those who had a terminal event during the observed time period. In regard to this, we present dynamic AIPCW estimating equations that provide an efficient estimation of regression coefficients, associated with smaller estimated variance. As a worked example, we apply the proposed approach to study the mean number of catheter-related bloodstream infections in heterogeneous patients with chronic intestinal failure who can possibly die. Here, we highlight the efficiency gain that results in narrower pointwise confidence intervals.

Cortese G., Scheike T. (2022). Efficient estimation of the marginal mean of recurrent events. Journal of the Royal Statistical Society-series C, 71:1787-1821. Cortese G., Scheike T. (2023). Regression models for recurrent events in presence of terminal events with efficient estimation.

WIN1.3 Dealing with competing risks in the analysis of recurrent events

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Recurrent events outcomes are frequent in both clinical and epidemiological studies and their analysis is often complicated by the presence of competing risks in the form of terminating events. A challenge is that a frequent terminating event will reduce the occurrence of the recurrent event and, thereby incorrectly, make a group appear more beneficial.
Several approaches to this challenge have been proposed, including:

1 Ignore it by treating terminating events as censoring
2 Ignore it by focusing on the recurrent events, only
3 Study a composite end-point consisting of both recurrent and terminating events and, thereby, reduce to a one-dimensional problem
4 Study a 'while alive' estimand and, thereby, reduce to a one-dimensional problem
5 Acknowledge that the outcome is, indeed, bivariate

A review will be given of these different approaches, recommending to treat the problem as a bivariate one. A method based on pseudo-values is applicable for this purpose. Furberg, J.K., Andersen, P.K., Korn, S., Overgaard, M., Ravn, H. Bivariate pseudo-observations for recurrent event analysis with terminal events. Lifetime Data Analysis (in press).

WIN2 INVITED SESSION

QUANTIFICATION OF SAFETY SIGNALS IN CLINICAL TRIALS: ESTIMAND, ESTIMATION, AND HOW WOULD GOOD LOOK LIKE IN TEN YEARS?

ORGANIZER | CHAIR : KASPAR RUFIBACH

WIN2.1 Principled approach to time-to-event endpoints with competing risks, with a focus on analysis of aes

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The assessment of safety is an important aspect of the evaluation of new therapies in clinical trials, with estimation of adverse event risk being an essential part of this. Standard estimators for such a probability of an adverse event (AE), such as the incidence proportion defined as the number of patients with a specific AE out of all patients in the treatment group of interest or one minus the Kaplan-Meier estimator of time-to-adverse event, do not account for varying follow-up times between arms and/or competing risks. Based on a sample of 17 randomized controlled trials (RCT) the SAVVY project (Survival analysis forAdVerse events with VarYing follow-up times, an academia – pharma consortium) aimed at quantifying the bias of several estimators of the AE probability. We will discuss common estimators of the AE probability and the assumptions they are making. Based on a sample of 186 AEs from the 17 RCTs we will empirically illustrate how large biases of various estimators can become for estimation of AE probabilities in one arm. In addition, the bias of estimators of relative AE risk between two arms will be quantified. We propose to use the Aalen-Johansen estimator to estimate AE risks, as it is a common nonparametric estimator of an event probability that properly accounts for varying follow-up times and competing risk that is implement in any standard software package. We will also discuss how key guidelines would need to be updated in light of our findings. Standard estimators of AE probabilities are biased up to a factor of five in the presence of varying follow-up times between patients or arms and/or competing risks. We advocate switching to the Aalen- Johansen estimator and to reflect this change in regulatory and reporting guidelines. More on SAVVY, incl. links to papers and markdown with code: https://numbersman77.github.io/savvy/

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WIN2.2 Estimands for safety – one size fits all?

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With ICH E9(R1), the estimand framework has made its way into practice for efficacy endpoints in clinical trials [1]. Discussions continue on the application of the estimand concept for exploratory analyses including safety.
Traditionally, most of clinical studies are designed in support of efficacy evaluations. In contrast to efficacy, safety objectives are in most cases rather unspecific and of exploratory nature. Unless specific safety topics are already identified, based on e.g. (pre-)clinical observations, class effects, or mode of action, safety objectives focus primarily on safety surveillance or signal detection. With accumulation of safety data for a medicinal product, more specific safety questions can be raised based on the evolving knowledge about risks potentially associated with treatment. While standard safety analyses primarily focus on the detection of potential risks, regulatory authorities expect at marketing authorization the latest, an identification, characterization and quantification of adverse reactions common enough to be detected in an appropriately large clinical trial safety database [2-5]. Criticism on standard safety analyses is not new. The estimand framework has contributed to a re- ignited discussion on the current practice of characterizing the safety profile during clinical development. Even if the status of a safety profile has not yet evolved to enable specific questions, the estimand concept can be helpful to inform discussions on study design and data retrieval. In this talk, I will critically evaluate the applicability of the estimand framework in the light of the different safety objectives and report on current status of discussions in the scientific community.

[1] ICH E9(R1) – Addendum on estimands and sensitivity analysis in clinical trials to the guideline onstatistical principles for clinical trials. November 2019. https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf, last accessed Feb 2023.
[2] ICH E1 – The extent of population exposure to assess clinical safety for drugs intended for longtermtreatment of non-life-threatening conditions. https://database.ich.org/sites/default/files/E1_Guideline.pdf, last accessed Feb 2023.
[3] FDA. Guidance for Industry – Premarketing risk assessment. March 2005.https://www.fda.gov/media/71650/download, last accessed Feb 2023.
[4] European Commission. Guideline on summary of product characteristics (SmPC). September2009. https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf, last accessedFeb 2023.[5] FDA. Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products— Content and Format. January 2006. https://www.fda.gov/media/72139/download, last accessed Feb2023.WIN2.2_ 48

WIN2.3 Adverse events with survival outcomes: from clinical questions to methods for statistical analysis

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When studying a novel treatment with a survival time outcome, failure can be defined to include an adverse event (AE) among the endpoints typically considered, for instance relapse. These events act as competing risks, where the occurrence of relapse as first event and the subsequent treatment change exclude the possibility of observing AE related to the treatment itself.
In principle, the analysis of AE could be tackled by two different approaches:
1. It requires a competing risk framework for analysis: the clinical question relates to the observed occurrence of AE as first event, in the presence of the event "relapse";
2. It requires a counterfactual framework for analysis: the clinical question relates to the treatment causing AE occurrence as if relapse could not occur.
This work has two aims: the first is to critically review the standard theoretical quantities and estimators with reference to their appropriateness for dealing with approaches 1 or 2 and to the following features: (a) estimators should address for the presence of right censoring; (b) theoretical quantities and estimators should be functions of time. The second aim is to define a strategy to relax the assumption of independence between the potential times to the competing events of the commonly used estimators when counterfactual approach 2 is of interest. After reviewing the standard methods[1] we clarify the impact of the crucial assumption of independence between potential times to competing events of the standard estimators used in the counterfactual approach. We propose the use of regression models, stratified Kaplan-Meier curves and inverse probability of censoring weighting[2] to relax the assumption of independence by achieving conditional independence given covariates and we develop a simulation protocol to show the performance of the proposed methods. The proposed methods overcome the problem due to the dependence between the two potential times. In particular, one can handle patients' selection in the risk sets, and thus obtain conditional independence between the two potential times, adjusting for all the observed covariates that induce dependence. The proposed methods can be also extended to the case of repeated adverse events.

[1] A. Allignol, J. Beyersmann, C. Schmoor (2016). Statistical issues in the analysis of adverse eventsin time-to-event data. Pharmaceutical Statistics, 15, 297-305
[2] S.J.W. Willems, A. Schat, M.S. van Noorden, M. Fiocco (2018). Correcting for dependent censoringin routine outcome monitoring data by applying the inverse probability censoring weighted estimator.Biometrical Journal, 62, 836-851

WIN2.4 Regulatory perspective on the analysis of safety in clinical trials and beyond

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From a regulatory perspective, the assessment of safety of new drugs is crucially important, as decision making is based on establishing that the benefit-risk balance is positive. This safety assessment goes well beyond estimation and quantification of signals from adverse events and laboratory data in clinical trials, and typically includes data, evidence and biological and pharmacological insights from a range of resources. By the very nature analysis and assessment includes signals on effects that were not foreseen, and hence cannot be a priori defined with the same rigor as estimands for primary efficacy outcomes. Nevertheless, estimation and quantification of the associated uncertainty (potential bias and variance) are important, and it is a long existing challenge that there has not been addressed statistically very well, while there is in principle no lack of methodology (e.g., in survival analysis). The estimand framework (1) projected on the analysis of safety data may help improve this, but it could be argued it does so because it highlights that the urgent improvement needed is proper estimation of comparative effects (irrespective of which estimand is targeted). In this presentation, I will explore current practice and pitfalls, what could be done to improve (jointly across the different stakeholders) and look ahead on how safety profiles are to be communicated (e.g. In SmPCs). I will also address potential use of external (real world data) in light of DARWIN-EU (2) and bridge to good practice guidance from pharmacoepidemiology (3).

(1) ICH E9(R1) – Addendum on estimands and sensitivity analysis in clinical trials to the guideline onstatistical principles for clinical trials. November 2019. https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf, last accessed Feb 2023.
(2) https://www.ema.europa.eu/en/about-us/how-we-work/big-data/data-analysis-real-worldinterrogation-network-darwin-eu
*(3) https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtmlWIN2.4_*