Marginal Structural Models to Analyse Causal Effects of Time-varying Treatments: an application to Osteosarcoma data

To date, it is still unclear what role is played by different combinations of cytotoxic drugs, drug dosages, and time to complete chemotherapy in regimens for osteosarcoma on survival outcomes. In analysing longitudinal data collected during randomised trials, particular attention is required due to the presence of a time-dependent confounder such as toxicity. This confounder is strictly patients related as a consequence of the exposure to cytotoxic agents. Both drug doses and starting date of the next chemotherapy cycle are dynamically allocated to each patient depending on the toxicity levels through to the end of the last cycle.

Data used in this study come from EURAMOS-1, a large study in resectable osteosarcoma which includes two randomised controlled trials. The aim of the trial is to determine the effect of post-operative chemotherapy based on histological response on survival outcomes. Administered dose of (up to) 5 drugs were recorded for each patient and for each cycle, as well as the CTCAE (Common Terminology Criteria for Adverse Events) grade for more than 20 different toxicities.

This research focuses on the role played by a specific cytotoxic agent on both histological response and survival outcomes. Answering these questions requires the use of ad-hoc statistical methodology such as Marginal Structural Models (MSMs).

MSMs can deal with both complexity and longitudinal nature of the data, and the delicate but crucial interplay between toxicity and allocated treatment. Under the main assumption of no unmeasured confounding, these models give unbiased estimates for the parameters of the model of interest (in this context logistic regression for the histological response and Cox proportional hazards regression model for survival outcomes) by using Inverse Probability of Treatment Weighting (IPTW). The effect of IPTW is to create a pseudo-population where

1. the allocated treatment is no longer confounded by toxicities

2. the causal parameters of interest are the same as in the true population.

In other words, unbiased estimates of the parameters of interest can be obtained by standard crude analysis on the pseudopopulation generated by IPTW.

In this talk we discuss how MSMs can be used to make robust inference about causal effects of time dependent treatments in clinical research when complex longitudinal data are available.