Designing a sequentially randomised study with adherence enhancing interventions for the first line treatment of diabetes

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Dynamic or adaptive treatment strategies can change treatment prescription over time in response to intermediate outcomes. A dynamic treatment regime thus stipulates at specific time points how treatment prescription should vary according to subject-specific measurements [1, 2]. Dynamic treatment regimes have shown to be valuable for the prevention of hypertension, treatment of depression, AIDS,... Adaptation of treatment happens over time because patients may become treatment resistent or overly sensitive, adherence may drop and/or the general health situation may develop in a way that requires a new therapeutic approach. When a cost-efficient treatment is available, adherence itself may become the target of an intervention. Sequentially randomized trials can then help evaluate how to best adapt adherence supporting interventions to past history of adherence and treatment response with the goal to optimize future treatment response through improved adherence, for instance in the prevention of HIV or first line treatment of diabetes.
Our goal here is to design a study to help control diabetes patients through adherence enhancement in a cost-efficient way. We wish to adapt the way in which we offer adherence support and care so the transition to a much more expensive second line treatment can be avoided or delayed. As a result, we plan to monitor patients through routine check-up visits and intervene only when observed HbA_{1c} levels increase above a certain set threshold. We thus consider a sequentially randomized trial to study adherence enhancing interventions involving education and social support, MEMS (Medication Event Monitoring Systems) with feedback or their combination. Specifically, a conditional factorial design is introduced at month 3 and at month 6 for patients whose HbA_{1c} has crossed the threshold at those times. We analytically compute the marginal effect of a policy of offering education and social support versus MEMS at month 3 and at month 6. We adapt the doubly robust estimator of Murphy, van de Laan and Robins [1] to this situation. Furthermore, we test for an effect of a given dynamic regime at the seperate and joint time points. We consider the impact on the study of pruning the double factorial design by deleting some treatment options e.g. avoid step-down arms. By simulation, we study the merits of different incomplete factorial designs, for finite sample sizes. This involves joint work with Robert Vander Stichele, Bart Van Rompaye, Bernard Vrijens and Johan Wens.

References

[1] Murphy, S.A., van der Laan, M.J. and Robins J.M. (2001), Marginal mean models for dynamic regimes, *Journal of the American Statistical Association*, **456 (96)**, 1410-1423.

[2] Murphy, S.A. (2005), An experimental design for the development of adaptive treatment strategies, *Statist. Med.*, **(24)**, 1455-1481