Reply to: Versatility of the clone-censor-weight approach: response to “trial emulation in the presence of immortal-time bias”

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We thank Zhao *et al.*[1] for their interest in our recent article[2] which aims to provide a step-by-step tutorial for the design and analysis of emulated target clinical trials from observational data, to prevent immortal-time bias. In particular, we would like to thank the authors for illustrating the versatility of the concept of cloning within the trial emulation framework by describing a wide range of applications.

In their letter, Zhao *et al.* provide a useful classification of causal questions for which the clone-censor-weight approach is appropriate. According to the proposed classification, this approach is useful (i) when time of treatment initiation begins after the entry in the study or the start of follow-up; (ii) when treatment strategies differ in duration or time of onset; and (iii) when treatment strategies are dynamic, such as treatment switching or successions of treatment strategies. They apply their classification to published studies where the clone-censor-weight method has been applied for comparative effectiveness research. In all three categories, grace period(s) need to be defined to reflect different intervals of time during which treatment may be received following each arm’s specific definition.

The categories differ by the role that time plays in the definition of the treatment strategies of interest. In the first category, the delay between entry in the study and treatment initiation is due to real-life constraints or disease management (e.g. neoadjuvant therapy) in treatment implementation, but the causal question of interest focusses on the treatment itself, rather than the time of treatment. On the contrary, in studies falling into the second category, timing is the key component of the causal question. However, in this category, timing is defined in reference to the start of follow-up, regardless of the evolution of individual characteristics over time (hence the name of static strategies). Finally, onset of treatment is also the main focus in studies belonging to the third category, but it is defined in reference to specific time-varying events, rather than the start of follow-up, making these treatment strategies dynamic.

Although this classification represents three different types of causal questions, we would like to emphasize that the steps we describe in our paper apply to all three. The definition of the ideal trial, inclusion criteria, causal contrasts of interests, etc. should always be made explicit. As highlighted in our original article, a clear presentation of the target trial of interest is paramount to avoid ill-defined observational studies.

[1] Zhao SS, Lyu H, Yoshida K. Versatility of the clone-censor-weight approach: response to “trial emulation in the presence of immortal-time bias”. *Int J Epidemiol*.

[2] Maringe C, Benitez Majano S, Exarchakou A, et al. Reflections on modern methods: trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol*. Published online May 9, 2020:dyaa057. doi:10.1093/ije/dyaa057