ESR Researcher Project: Non-technical Summary

"Subgroup analyses in early-phase clinical trials"

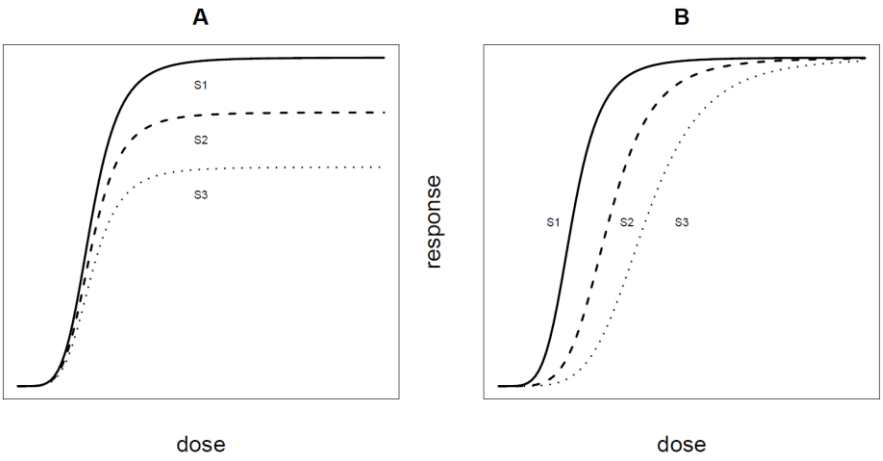
Team: Marius Thomas, Björn Bornkamp

The identification of patient subgroups (defined in terms of baseline covariates or biomarkers) with a modified response to a treatment is an important task in drug development. Identifying such subgroups of patients is essential to personalize medicine and guarantee, that every patient receives the best possible treatment. It is however also a very challenging challenging task. The identification task itself is not trivial: Many biomarkers will be prognostic, but usually one is interested in covariates or biomarkers modifying the response to the specific treatment administered (predictive covariates/biomarkers). Additionally the number of possible subgroup-defining covariates and biomarkers is often large, which increases the chance of false positive findings [1]. It is therefore generally recommended to prespecify the analysed subgroups if possible and check subgroup results for biological plausibility [2].

In addition there is a need for statistical methods, that can deal with the challenges of subgroup analyses and provide results, that are reliable and can be used to determine if a subgroup exists or if the finding can be considered spurious. Many such methods have been proposed in the statistical literature, however most of them focus on trials with two treatment arms, where patients are either assigned to a placebo group or a group receiving one dose of the treatment.

Clinical trials with more than two arms with multiple doses of the same treatment have been somewhat neglected in the literature on subgroup identification. In such trials one is often interested in estimating the dose-response relationship to decide on an efficacious and safe dose for the treatment. As part of our project we developed methods for subgroup identification for such dose-response trials. With our methods it is possible to identify subgroups with different dose-response curves. Therefore we can not only identify subgroups, where the dose-response curve is raised or lowered (A) but also subgroups, where the dose-response curves are horizontally shifted (B) (please see the figures on the following page).

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.



This allows us to not only identify subgroups with a different treatment effect, but also subgroups, where it could be advisable to choose a different dose. For more details see our publication [3].

References

[1] Lagakos, S. W. (2006). The challenge of subgroup analyses—reporting without distorting. *New England Journal of Medicine*, *354*(16), 1667-1669.

[2] EMA guideline on the investigation of subgroups in confirmatory clinical trials. 2014. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500160523.pdf (accessed 29 May 2018)

[3] Thomas, M., Bornkamp, B., & Seibold, H. (2018). Subgroup identification in dose-finding trials via model-based recursive partitioning. *Statistics in medicine*, *37*(10), 1608-1624.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.