ESR Researcher Project: Non-technical Summary

"Dose finding for combination trials with many treatments"

Team: Pavel Mozgunov, Thomas Jaki

The primary motivation of the project is the growing complexity of early phase clinical trials. It starts to become common to consider more complex dosing regimens rather than doses of a single agent. For instance, therapies using a combination of drugs have become the mainstream approach to diseases such as cancer and tuberculosis. However, the combination context gives rise to additional challenges.

A lot of single-agent dose finding trials are based on the assumption "the more the better" - the toxicity of the drug increases with the dose. This means that one can naturally order doses according to the monotonically increasing toxicity. This might not hold for combinations. Consider the combination of two agents in which one combination has a higher dose of the first compound, but a smaller dose of the second compound. In the vast majority of trials, one cannot define which of these combinations is more toxic prior to the study. Finally, the problem of unknown ordering of toxicities also appears in single-agent studies of molecularly targeted agents (MTA). For MTAs either dose-efficacy or dose-toxicity relationships can have a plateau or a dose-efficacy relationship can exhibit an umbrella shape.

The problems in these clinical trials are similar in their nature as they suffer from the unknown ordering of dosing regimens. Additionally, study toxicity and efficacy endpoints in an integrate Phase I/II clinical trial is becoming common as well. To conduct more complex clinical trials, specific methods were developed in the course of work of the project.

A novel criterion to govern the selection of dosing regimens in clinical trials was obtained. It was found that the criterion minimises the uncertainty in a dose finding experiment subject to the constraint to allocate as much as possible patients to the dosing regimen with the best characteristics defined by a clinician. The proposed criterion is generic and can be applied to trials with multinomial outcomes including, for examples, Phase I trials with binary toxicity and Phase I/II trials with binary toxicity and efficacy endpoints. It was found that a high probability of correct selections can be achieved without any parametric or monotonicity assumption due to specific properties of the criterion. It was found that the Phase I design employing the novel criterion performs comparably or outperforms the currently used in practice methods (Mozgunov and Jaki, 2018a). This criterion was also used to develop a novel Phase I/II design for an ongoing combination-schedule oncology trial (Mozgunov and Jaki, 2018b). The main challenge faced by clinicians was that they could not order the combinations according to increasing toxicity and efficacy. This resulted in an infeasible parametric model which could not be used with a limited sample size. The proposed design not employing parametric assumption was found to be a high performing candidate for such trials and resulted in a high probability of correct selections under a variety of clinically relevant scenarios.

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.

The proposed criterion is generic and can be also applied to govern a selection in well-established model-based dose finding design, for example, Continual Reassessment Method (O'Quigley et al., 1990). It was found that the use of the criterion can lead to either (i)~fewer number of patients experienced adverse events during the trial, but the similar probability of correct selections or (ii) a similar number of adverse events as the Escalation with Overdose Control approach (Babb et al. 1998, widely employed by pharmaceutical companies), but in a significantly higher probability of correct selections of the dose for further trials.

Finally, it was found that the proposed criterion can be useful beyond the dose finding and was successfully applied to benefit-risk assessment as a criterion for Multi-Criteria Decision Analysis.

References

Babb, James, Rogatko, Andre and and Zacks, Shelemyahu (1998) Cancer phase I clinical trials: efficient dose escalation with overdose control. Statistics in Medicine 17(10), 1103–1120.

Mozgunov, Pavel and Jaki, Thomas (2018a) An information-theoretic approach for selecting arms in clinical trials. arXiv:1708.02426

Mozgunov, Pavel and Jaki, Thomas. (2018b). An information-theoretic phase i/ii design for molecularly targeted agents that does not require an assumption of monotonicity. arXiv:1803.04397.

O'Quigley, John, Pepe, Margaret and Fisher, Lloyd. (1990). Continual reassessment method: a practical design for phase 1 clinical trials in cancer. Biometrics, 33–48.

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.