

Multiple Testing in Stratified Cancer Trials

Research Objective

To develop methods to control the family wise error rate while testing multiple hypotheses in biomarker-stratified cancer clinical trials.

Motivation and Novelty

Stratified medicine is a rapidly evolving area in clinical research as it offers an essential paradigm for personalised therapeutics. Statistical methodology to address this stream is not yet robust. Biomarker-stratified clinical trials assess the biomarker signature of subjects and split them into subgroups so that treatment is of benefit to those who are likely to respond. Since multiple hypotheses are tested, it becomes important to control the type I error. Current methods control the false positive rate where one rejects the null hypothesis while in reality that was true. For two subgroups, the false positive rate is controlled across the two hypotheses as a Family Wise Error Rate (FWER) to an overall predetermined significance level.

The concept of “Wrong Positive” rate has recently been proposed where one rejects the null hypothesis in one subgroup while in reality the efficacy would be in the other subgroup. Controlling the wrong positives as well as false positives to an overall significance level constitutes a strong FWER. Further options exist for control of Individual Outcome FWER by assigning weighting to reject the respective null hypotheses. This methodology has been applied for an optimal biomarker-stratified Simon two-stage oncology trial design. The research project shall investigate further the methods for strong and weak control of FWER with or without controlling the individual hypotheses and illustrate the variation in minimum expected sample sizes for a variety of designs for biomarker-stratified clinical trials. The FWER options thus obtained would provide a natural choice for Phase II as well as confirmatory trials of anti-cancer drugs.

Methods and deliverables

- Gain understanding of clinical trial statistical methodology with a focus on biomarker-stratified cancer trial designs.
- Critically evaluate the current methods for FWER control.
- Develop novel strategy for controlling FWER for multiple hypotheses testing across stratified designs – fixed as well as adaptive / group sequential.
- Compute probability of outcomes for different FWER options.
- Perform simulations that yield novel designs for chosen operating characteristics.

Who will benefit?

Cancer patients, Oncologists, Researchers in Stratified Medicine

Follow-up PhD project

A successful completion of the mini-project shall pave the way for developing novel statistical methodology of biomarker-stratified designs in cancer clinical trials from both a frequentist’s point of view as well as Bayesian. Of late there has been an abundance of prognostic biomarker data that could be the predictive biomarker data in the near future. There is, therefore, greater need to be methodologically equipped to deliver biomarker-stratified healthcare interventions. The PhD project is likely to get involved in the FOCUS4 trial in collaboration with the Birmingham School of Cancer Sciences.

References

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3. Jennison C, Turnbull, BW. *Group sequential methods with applications to clinical trials.* Chapman & Hall / CRC, 2000.

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