Comparing Approaches to Treatment Effect Estimation for Subgroups in Clinical Trials

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IDEAS Think Tank
Traunkirchen, June 23rd, 2016
Outline

- Introduction
- Methods for Adjusted Treatment Effect Estimation in Subgroups
  - Model averaging
  - Resampling
  - Lasso
- Simulation Study
Focus of this presentation

*Exploratory subgroup analysis*

- Fully Confirmatory Setting (out of scope for today)
  - Pre-specification of subgroups
  - Multiple testing strategy in place
  - Adequate sample size for subgroup

- **Exploratory subgroup analysis**
  - Routinely performed in early phase (e.g. proof-of-concept, Phase IIa/b studies) but also on an exploratory basis in late stage trials
  - Sample size: Comparisons in candidate subgroups not „powered“
  - Pre-specification of subgroups?
    - Usually a list of subgroup defining covariates is pre-defined
  - How many covariates?
    - ~5-30
Subgroup analyses

Statistical model for normally distributed endpoints

Subgroup analysis model

Data model: \( y_i \sim N(\mu_i, \sigma^2), i=1, \ldots, n \)

\[ \mu_i = \beta_0 + \beta_2 s_i + (\beta_1 + \beta_3 s_i) T_i \]

- \( \mu_i \) – Mean response of patient i
- \( T_i \) – Treatment indicator
- \( s_i \) – Subgroup indicator (1 in the subgroup, 0 in the complement)
- \( \beta_0 \) – Placebo effect
- \( \beta_1 \) – Treatment effect
- \( \beta_2 \) – Prognostic effect of subgroup (independent of treatment)
- \( \beta_3 \) – Predictive effect of the subgroup (change in the treatment effect)

With this approach there is one model for each subgroup indicator
Subgroup analyses

Common approach for identifying subgroups

\[ y_i \sim N(\mu_i, \sigma^2), \ i=1, \ldots, n \]
\[ \mu_i = \beta_0 + \beta_2 s_i + (\beta_1 + \beta_3 s_i) T_i \]

- For all potential K subgroups (i.e. subgroup indicators)
  - fit the model and obtain treatment effect in subgroup: \( \hat{\beta}_1^{(k)} + \hat{\beta}_3^{(k)} \)
  and a p-value for testing \( \beta_3^{(k)} = 0 \) ("interaction test")
  - Choose model/subgroup, based on
    - magnitude of \( \hat{\beta}_1^{(k)} + \hat{\beta}_3^{(k)} \) for different subgroups k
    - on the p-value for the interaction test

- Naive estimates \( \hat{\beta}_1^{(k)} + \hat{\beta}_3^{(k)} \) will be overly optimistic due to selection bias
Treatment Effect Estimation: Methods
1. Model Averaging
Model averaging

Motivated from Bayesian ideas

- Subgroup Selection can be viewed as Model Selection*
- Each subgroup defines a different statistical model
- Picking one model (e.g. with high or the highest (standardized) treatment effect) ignores model uncertainty
  - This is equivalent to setting the posterior model probabilities to 1 for one model and 0 for all others
  - Idea of model averaging: Use weighted inference based on the posterior model probabilities for each model/subgroup

Model averaging

*In a subgroup analysis setting*

- Assume a set of $K$ candidate subgroups is pre-specified
  - Candidate subgroups $s^{(1)}, \ldots, s^{(K)}$

- These correspond to $K$ candidate models $M_1, \ldots, M_K$
  - the $k$-th model is given by

$$
y_i \sim N(\mu_i^{(k)}, \sigma^{(k)}_2)
$$

$$
\mu_i^{(k)} = \beta_0^{(k)} + \beta_2^{(k)} s_i^{(k)} + (\beta_1^{(k)} + \beta_3 s_i^{(k)}) T_i
$$

with prior distributions for $\beta_0^{(k)}, \beta_1^{(k)}, \beta_2^{(k)}, \beta_3^{(k)}$ and $\sigma^{(k)}_2$

and prior model probabilities for $M_1, \ldots, M_K$
Model averaging

In a subgroup analysis setting

- For subgroup $s^{(k)}$ under model $M_k$
  - The treatment effect in the subgroup is $\beta_1^{(k)} + \beta_3^{(k)}$ (naive estimate)
  - The treatment effect in the complement is $\beta_1^{(k)}$

- Now also estimate the treatment effect for subgroup $s^{(k)}$
  under model all other models $M_{k'}$ (with $k' \neq k$)

- Then take the weighted average over all models with posterior model probabilities as weights
  - Amount of shrinkage depends on how posterior model probability is distributed across models
2. Resampling
Resampling

Idea*

1. Split data into training (identification) and test (estimation) sample

2. Perform subgroup identification on the training data

3. Compare the treatment effect in the selected subgroup in the training and test data set and adjust original estimate

*Sun, L. et al (2005), Genet Epidemiol., 28, 352-367
Resampling

How to come up with a treatment effect estimate

- Implementation using bootstrapping
  - Perform selection of a subgroup in bootstrapped sample
  - Calculate treatment effect estimate in selected subgroup based on identification sample and out-of-bag sample (test sample)

- Three ways to adjust treatment effect estimates
  1. Bias estimation („rsbias“)
  2. .632 bootstrap estimator („rs632“)
  3. Combining model averaging and resampling („rsma“)
3. Penalized multivariate regression: LASSO
Penalized multivariate regression: LASSO

- Multivariate regression model including all covariates
  \[ \mu_i = \beta_0 + \sum_{k} \beta_{2,k} x_i^{(k)} + (\beta_1 + \sum_{k} \beta_{3,k} x_i^{(k)}) T_i \]

- This model can get unstable to fit (if n is small compared to K) and clearly it would be overfitting data

Lasso regression to shrink parameters
  - Shrinks some of the \( \beta_{2,k} \) and \( \beta_{3,k} \) to zero
  - Induces shrinkage to the overall treatment effect
How to obtain treatment effect estimate for a given subgroup?

- Predict treatment effect for every patient in the subgroup based on the LASSO model
- Average this over all patients in the subgroup

Shrinkage towards overall effect

- Will be induced by the fact that many of the $\beta_{3,k}$ will be estimated to be 0 → the corresponding covariate for this subgroup will have no effect
Simulation Study
Simulation Setup

- Generate K covariates from N(0,1)-distribution

- Model for outcomes:

\[ y_i = g(x_{1,i})T_i + \varepsilon_i, \varepsilon_i \sim N(0,1) \]

  - First covariate x1 is predictive
  - Different functional forms for \( g \): step function, linear, sigmoidal
  - No prognostic covariates

- Simulate 5000 trials and identify the best subgroup for each trial. Then estimate the treatment effect for the identified subgroup
Results

Bias for estimating the treatment effect in the *selected* subgroup (n=50)
Results

MSE for estimating the treatment effect in the **selected** subgroup (n=50)
Conclusions

- Naive treatment effect estimates for identified subgroups suffer from selection bias

- We compared several different approaches to adjusted treatment effect estimation through extensive simulations

- Several viable alternatives to naive estimates
  - Model averaging, Resampling (rsma, rs632), Lasso
  - Estimators have smaller biases, MSEs and better CI coverage under all considered scenarios
References


Acknowledgements

This work was supported by funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567 and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 999754557. The opinions expressed and arguments employed herein do not necessarily reflect the official views of the Swiss Government.