Subgroups analyses
Sins or Opportunities

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The old view :
Best treatment to treat a large population

- Considers an average effect of the treatment for medical decisions
- « One size fits all » approach

Profound changes in the conception of diseases. Leading to the concepts of precision medicine

- Patients with the « same » disease have not the same disease.
- The same disease has not the same consequences for every types of patients (ex. molecular host-tumor interactions in cancer)
- The same treatment has not the same effect in every patients (i.e pharmacogenetics..)
- ------→ Find the best the treatment for a subgroup of patients

However:

- Subgroup analyses have been generally excluded of good practices for evidence-based medicine for several reasons:
  - Data –derived hypotheses
  - Inflation of alpha.

Sins

- Treatment effect in one subgroup : Make a new RCT !

Challenges in subgroup analyses.

- Disregarding a relevant subpopulation a treatment option may be missed due to a dilution of the treatment effect in the full population.

- Even if the diluted treatment effect can be demonstrated in an overall population, it is not ethical to treat patients that do not benefit from the treatment when they can be identified in advance.

- Selecting a spurious subpopulation increases the risk to restrict an efficacious treatment to a too narrow fraction of a potential benefiting population.

(Graf A et al. Biometrical J 2015)

Controlling Familywise error rate FWER

- Methods exist for traditional RCTs when subgroups are defined *a priori*
  - Closed testing procedures
  - Bonferronni derived methods
  - Simes'test

  …

  No sin for subgroup analyses when appropriate methods are used.

Opportunities : Adaptive trials

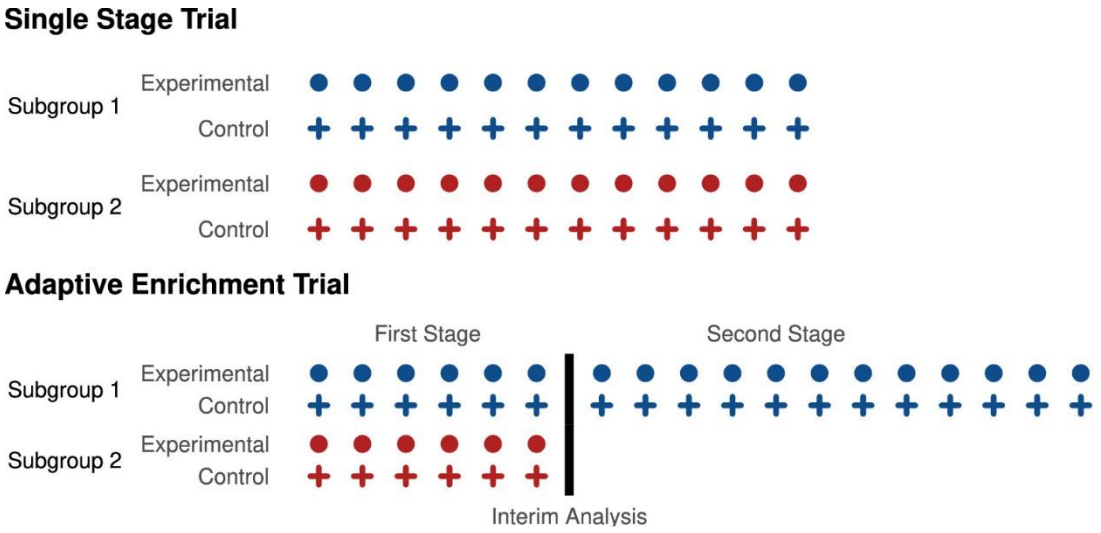
Adaptive Design is: A clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.
FDA Guidance **NOVEMBER 2019**

- In Personalized Medicine the most common adaptations during the implementation of adaptive designs refer **to changes in randomization probabilities within the biomarker-defined subgroups or dropping a biomarker-defined subgroup**

- Advantages: Better « signal/noise » ratio.

Opportunities : Adaptive enrichment designs

- Use of interim data in selecting the target population for the remainder of the trial, either continuing with the full population or restricting recruitment to the subset of patients.

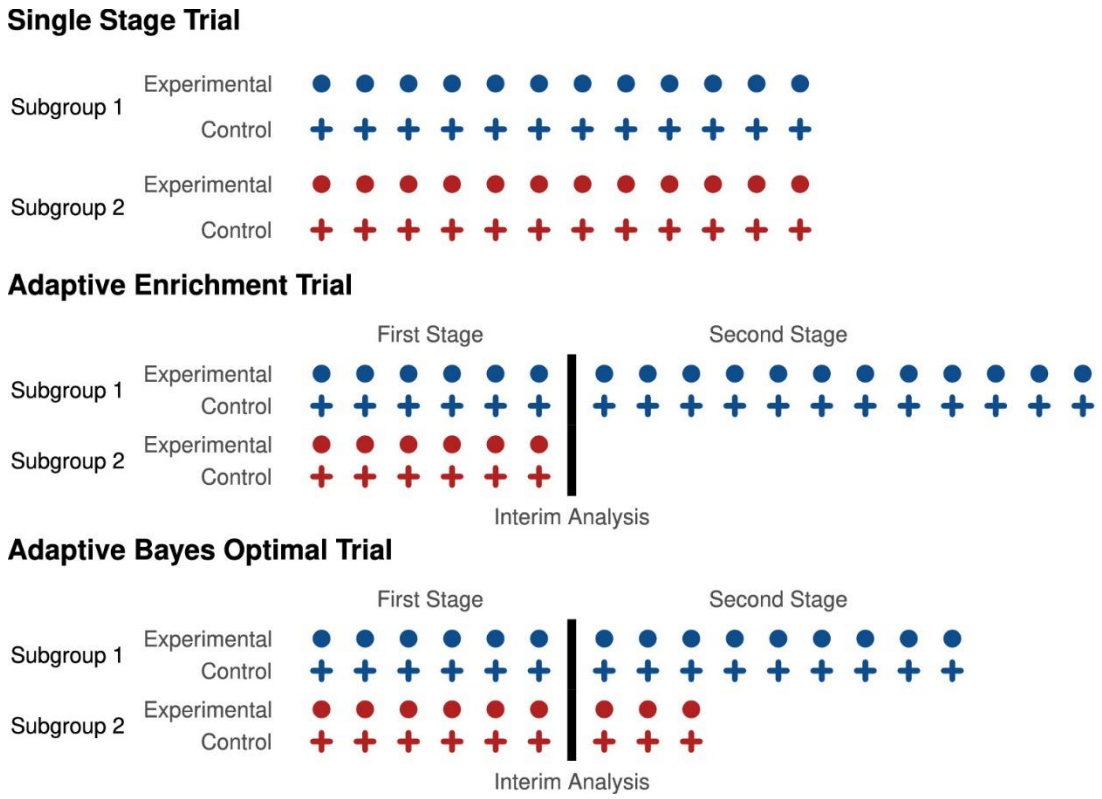


Statistical challenges

- Bias ?
- Inference on treatment effect based on both stages or only second stage ?
- Maintenance of FWER

Opportunities

Changing recruitment probability in each subgroup at interim analysis



- Ballarini et al. (Stat Med 2020) combined frequentist approach to control FWER and Bayesian decision-theoretic framework that **maximize an utility function (U)**
- U can takes the population **prevalence of subgroups** into account.
- Or **the gain** to reject the the null hypothesis in the full population or in the subgroup .
- Sponsor view and Public health view may be **incorporate in the formalism of the utility function** (see Graf A. et al. Biometrical J 2015)

Opportunities :

Combining **identification of subgroups** based on a large number of covariables and **treatment effect estimation** (see Loh 2018)

Methods

- Interaction trees (Su et al.2009)
- SIDES (Lipkovich 2011)
- Virtual twins (random forest, Foster et al 2011)
- GUIDE (Loh,2009) Generalized unbiased interaction detection and estimation.
- MOB (Seibold 2016)
- FindIT (Imai 2013)
- ROWSi (Xu 2015)
- PRIM (Chen 2015)
- SeqBT (Huang 2017)
- OWE (Chen 2017)

Problems (non exhaustive list)

- Bias in selection of subgroup variables
- False discovery
- Identification of correct predictive variables
- Bias in estimates of subgroup treatment effects
- Subgroup stability

Opportunities: Adaptive enrichment designs. For **Continuous Biomarkers**

- Allows **the choice of a threshold value** for one single biomarker on the first stage and to continue with subgroups above this threshold.

- Subgroups are nested .

- Stallard N (Biometrics 2021) proposed methods for selection of K subgroups in stage I maintaining familywise type 1 error rate

Conclusions

- Using recent advances in statistical methods

  - Opportunities > Sins