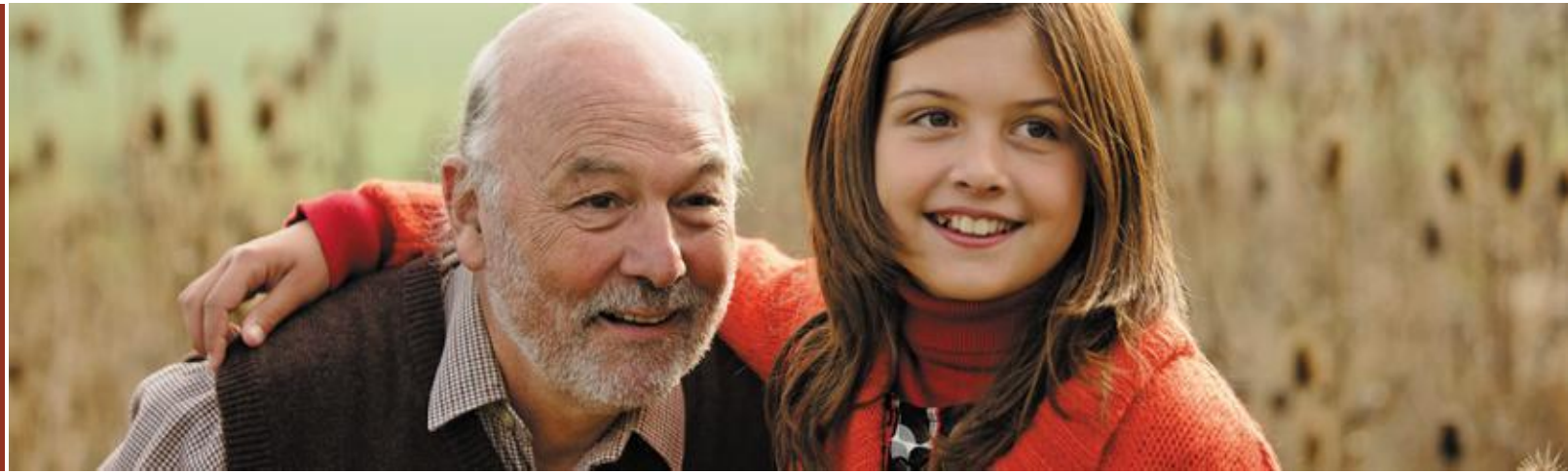

Selection and estimation in exploratory subgroup analyses – a proposal

Gerd Rosenkranz, Novartis Pharma AG, Basel, Switzerland

EMA Workshop, London, 07-Nov-2014

NOVARTIS
PHARMACEUTICALS

Purpose of this presentation

- Proposal for exploratory subgroup analyses
  - Favoring estimation over tests and/or p-values
- Identification of subgroups with differing efficacy (‘predictive subgroups’) as an integral part of analysis
  - Accounting for subgroup selection uncertainty and selection bias
- Discussion of properties, limitations and extensions
- *General remark: The potential of any method of subgroup analysis is limited by the information content of the data*

Definition of Subgroups

Draft EMA Guideline on Subgroups in confirmatory trials, Section 4.1

- A **subgroup** can be defined as any subset of the recruited patient population that fall into the **same category** (level) with regard to **one or more descriptive factors** prior to randomization
- Factors may relate to
  - Demographic characterstics (e.g., age, gender, race)
  - Disease characteristics (e.g., time of diagnosis, severity)
  - Clinical considerations (e.g., region, concomitant medication)
- Subgroups defined by different factors may **overlap**
- Sufficient to consider subgroups based on a **single factor** in most cases

Consistency

- Evidence for **lack of consistency** if at least one subgroup can be identified where the effect of test treatment over control differs
  - from the overall effect or, equivalently,
  - between subgroup and its complement
- How to identify subgroups without too much risk of chance findings or incorrect selections?
- How to estimate the effect in the identified subgroups without too much bias?
- What constitutes sufficient evidence of **consistency** is less obvious

A modeling approach for subgroup identification

- Assume subgroups can be defined in terms of **factors with two levels**, that is, each factor divides the patient population into **two subgroups** like
  - Gender: male, female
  - Age group: $\leq 65y, > 65y$
- List of candidate factors available
- Turn subgroup identification into model selection
  - For each candidate factor, fit a statistical model including a term that reflects the amount by which the difference in treatment arms is influenced by the factor
  - Select the model providing the **best fit** and **estimate** the amount by which the difference in treatment arms is influenced by the factor

A modeling approach for subgroup identification

- Drawbacks
  - Does not account for model **selection uncertainty**
  - May result in **biased estimates** (driven by search for the best fit)
  - Small changes of data may result in substantially different results
- Better but expensive approach:
  - Identify factor corresponding to best fit in a **series of studies**
  - Note how often different factors are identified
  - **Aggregate estimates** across studies
- Consider re-sampling instead

A modeling approach for subgroup identification

1. Sample with replacement (by treatment) from original data
2. Identify model with best fit to sample
3. Obtain estimates from that model
4. Repeat steps 1 – 3 above many times
5. Select the factor belonging to the most frequently selected model (‘voting’)
6. Obtain (biased-reduced) parameter estimates for that selection from the samples

Simulations

Assumptions

- Normally distributed data with $\sigma = 1$
- Overall difference between test and control: 0.5
- 90% power, $\alpha = 0.00125$ (two trials in one)
- 1:1 randomization
- 166 subjects per treatment
- Two predictive factors: ‘gender’ and ‘age group’, such that each gender – age group combination accounts for 25% of subjects
- Three unpredictive factors called random1, random2, random3 that mark subgroups randomly
- Effect of control $= 0$ (regardless of subgroups)
- Effect of test treatment in subgroups on following slides
- 500 simulated studies with 200 re-samples each

Simulation results

Consistent effects

Consistent mean effect of test treatment		Gender		Marginal	Difference
		0	1		
Age group	0	**0.5**	**0.5**	0.5	**0.0**
	1	**0.5**	**0.5**	0.5	
Marginal		0.5	0.5	**0.5**	
Difference		**0.0**			

Factor	Frequency of selection (%)	True marginal difference	Estimator	Bias-reduced estimator
Age group	21.0	**0.0**	-0.02(0.35)	-0.02(0.25)
Gender	18.0	**0.0**	-0.06(0.29)	-0.05(0.21)
Random 1	19.8	0.0	0.07(0.34)	0.04(0.21)
Random 2	19.0	0.0	0.02(0.38)	0.02(0.27)
Random 3	22.2	0.0	0.01(0.40)	0.02(0.28)

Simulation results

Inconsistent effects

Inconsistent mean effect of test treatment		Gender		Marginal	Difference
		0	1		
Age group	0	**0.2**	**0.4**	0.3	**0.4**
	1	**0.5**	**0.9**	0.7	
Marginal		0.35	0.65	**0.5**	
Difference		**0.3**			

Factor	Frequency of selection (%)	True marginal difference	Estimate	Bias-reduced estimate
Disease status	**61.6**	**0.4**	0.48(0.21)	0.41(0.21)
Gender	**27.0**	**0.3**	0.45(0.25)	0.37(0.23)
Random 1	3.8	0.0	-0.03(0.45)	-0.01(0.35)
Random 2	2.8	0.0	-0.15(0.39)	-0.12(0.30)
Random 3	4.8	0.0	0.03(0.55)	0.02(0.42)

Remarks

- Approach can be extended to
  - Binary and (ordered) categorical **endpoints**
  - Continuous **factors** (covariates)
- Need to account for subgroups defined by more than one factor if effect in a subgroup strongly affected by another factor:

Inconsistent mean effect of test treatment		**Gender**		Marginal	**Difference**
		0	1		
Age group	0	**0.3**	**0.7**	0.5	**0.0**
	1	**0.7**	**0.3**	0.5	
Marginal		0.5	0.5	**0.5**	
Difference		**0.0**			

NOVARTIS

Outlook

- Proposed method can be further extended to derive a **predictor** for the **effect of treatment** in a **future patient**
- Can use the factor values directly – no need to **artificially dichotomize** numerical factors (like age, BMI) to define subgroups with all its disadvantages
- **Predicted effect size** under alternative treatments and measure of prediction uncertainty can **support physician's decision** on how to treat a patient