Subgroup Screening

Explore Treatment Effect Heterogeneity in Clinical Trials

Richard C. Zink, PhD
Principal Research Fellow
JMP Statistical Discovery LLC

Adjunct Professor
Department of Biostatistics
University of North Carolina at Chapel Hill
richard.zink@jmp.com

Subgroup Analyses

- Describe the potential for differential response within important demographic, genetic, disease, environmental, behavioral, or regional characteristics
- From a regulatory perspective, show that the estimated overall effect is broadly applicable to patients, particularly when the study population is heterogeneous
- Generate hypotheses for future research
- Even if not presented within individual clinical trials, subgroup analyses are expected within integrated efficacy and analyses for development programs for major demographic and disease characteristics

Subgroup Analyses

- 524/1082 (48.4%) clinical trials reported subgroup results
  - 156 (30%) reported a single subgroup
  - 90 (17%) reported 2-3 subgroups
  - 73 (14%) reported 4-5 subgroups
  - 205 (39%) reported 6 or more subgroups
- Most common subgroups
  - Age
  - Sex
  - Race
  - Major disease characteristic
  - Body mass index
  - Geography
  - Smoking status

Wei L, Butterly E, Rodríguez Pérez J, et al. (2024). Description of subgroup reporting in clinical trials of chronic diseases: A meta-epidemiological study. *BMJ Open* 14:e081315 1-10.

Subgroup Analyses

- Transparency is key
  - Subgroup size
  - Number of subgroups assessed compared to those reported
  - Determined pre- or post-hoc
  - Whether multiplicity adjustments were applied
  - Whether stratified randomization was used
  - Whether heterogeneity was formally assessed
- Subgroup size is often not within the control of the sponsor

Subgroup Analyses

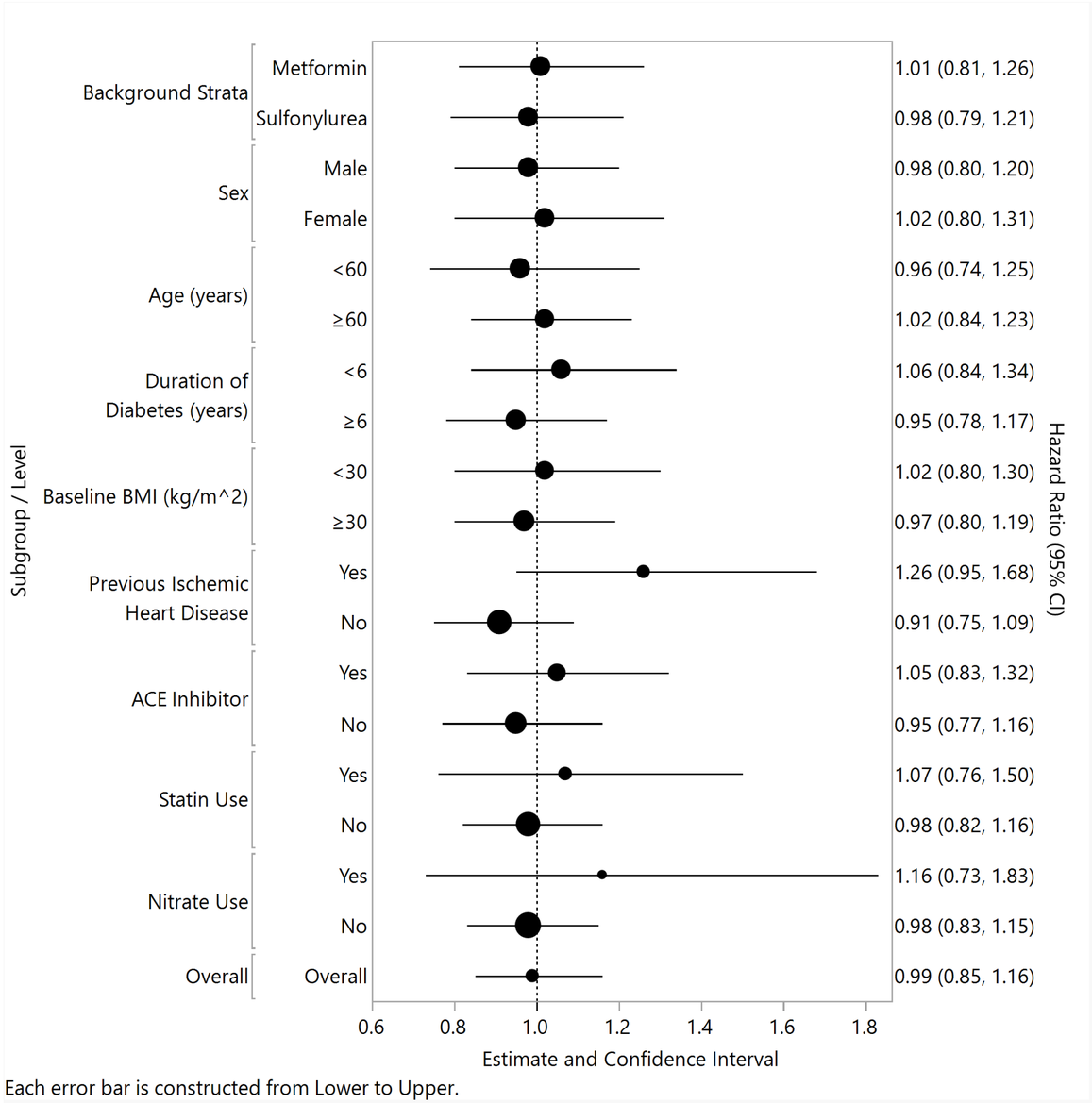
Definitions

- **Factor**: variables (columns). For example, Sex at Birth
- **Subgroup**: levels or combination of levels from one or more factors. For example, Male, Female. When considered with an age factor:
  - Males, < 65 Years
  - Males, ≥ 65 Years
  - Females, < 65 Years
  - Females, ≥ 65 Years

Subgroup Analyses

Challenging to Produce!

- **BY** analyzes combinations of factors levels, but not the individual levels
- Need to run a platform 10 times with different **BY** specifications
  - ACE Inhibitor
  - Age (years)
  - Background Strata
  - Baseline BMI (kg/m^2)
  - Duration of Diabetes (years)
  - Nitrate Use
  - Previous Ischemic Heart Disease
  - Sex
  - Statin Use
  - Overall (no subgroups)



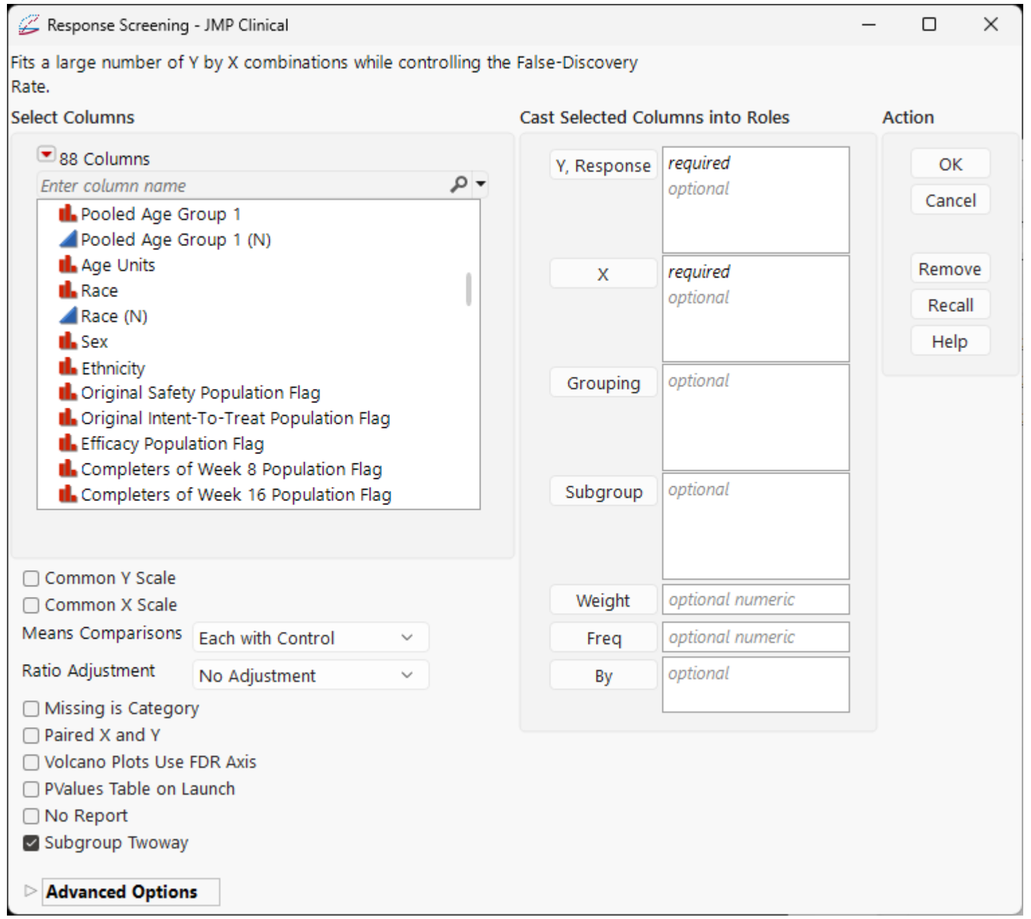
Each error bar is constructed from Lower to Upper.

Home PD, Pocock SJ, Beck-Nielsen H, et al. (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open label trial. *Lancet* 373: 2125 2135.

Subgroup Analyses

Response Screening to the Rescue!

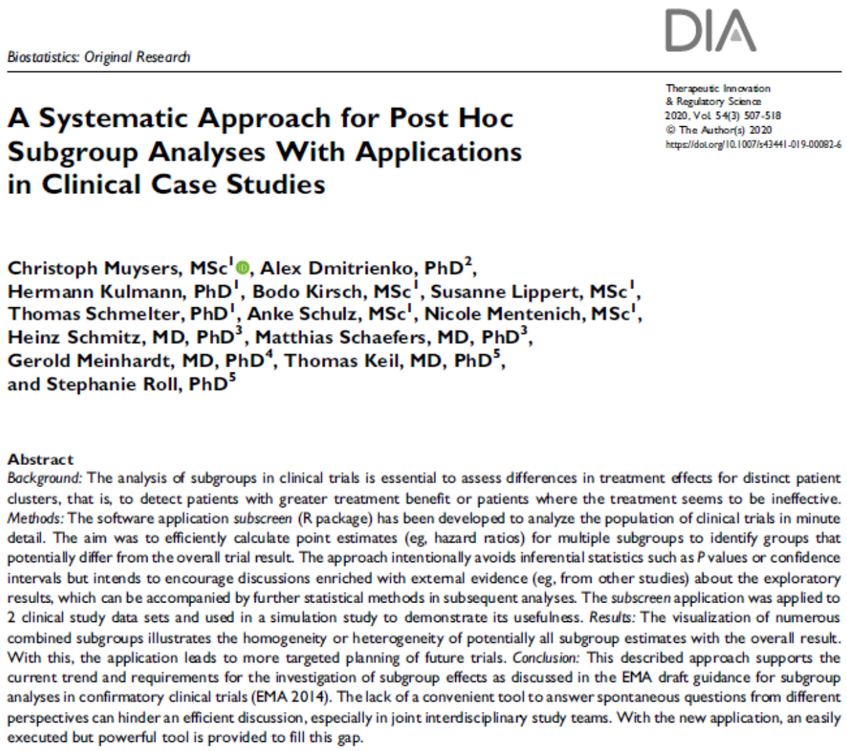
- The **Subgroup** role in Response Screening produces these results with a single call
  - ACE Inhibitor
  - Age (years)
  - Background Strata
  - Baseline BMI (kg/m^2)
  - Duration of Diabetes (years)
  - Nitrate Use
  - Previous Ischemic Heart Disease
  - Sex
  - Statin Use
  - Overall (no subgroups)
- Checking **Subgroup Twoway** produces additional subgroups based on combinations of two factor levels (e.g., diabetic males)
- Note: can supply a continuous variable as a factor!



Subgroup Screening

Definitions

- New feature in JMP Clinical 19 that allows users to explore an endpoint within subgroups to assess treatment effect heterogeneity
- Produces suggested analysis from *TIRS*
- Bayer statisticians using R Shiny



Biostatistics: Original Research

DIA

Therapeutic Innovation & Regulatory Science
2020, Vol. 54(3) 507-518
© The Author(s) 2020
https://doi.org/10.1007/s43441-019-00082-6

A Systematic Approach for Post Hoc Subgroup Analyses With Applications in Clinical Case Studies

Christoph Muysers, MSc[1], Alex Dmitrienko, PhD[2], Hermann Kulmann, PhD[1], Bodo Kirsch, MSc[1], Susanne Lippert, MSc[1], Thomas Schmelter, PhD[1], Anke Schulz, MSc[1], Nicole Mentenich, MSc[1], Heinz Schmitz, MD, PhD[3], Matthias Schaefers, MD, PhD[3], Gerold Meinhardt, MD, PhD[4], Thomas Keil, MD, PhD[5], and Stephanie Roll, PhD[5]

Abstract

Background: The analysis of subgroups in clinical trials is essential to assess differences in treatment effects for distinct patient clusters, that is, to detect patients with greater treatment benefit or patients where the treatment seems to be ineffective. *Methods:* The software application *subscreen* (R package) has been developed to analyze the population of clinical trials in minute detail. The aim was to efficiently calculate point estimates (eg, hazard ratios) for multiple subgroups to identify groups that potentially differ from the overall trial result. The approach intentionally avoids inferential statistics such as *P* values or confidence intervals but intends to encourage discussions enriched with external evidence (eg, from other studies) about the exploratory results, which can be accompanied by further statistical methods in subsequent analyses. The *subscreen* application was applied to 2 clinical study data sets and used in a simulation study to demonstrate its usefulness. *Results:* The visualization of numerous combined subgroups illustrates the homogeneity or heterogeneity of potentially all subgroup estimates with the overall result. With this, the application leads to more targeted planning of future trials. *Conclusion:* This described approach supports the current trend and requirements for the investigation of subgroup effects as discussed in the EMA draft guidance for subgroup analyses in confirmatory clinical trials (EMA 2014). The lack of a convenient tool to answer spontaneous questions from different perspectives can hinder an efficient discussion, especially in joint interdisciplinary study teams. With the new application, an easily executed but powerful tool is provided to fill this gap.

Subgroup Screening

- A continuous or binary endpoint with response screening
- Demo
  - CDISC SDTM-ADaM Pilot Study
  - Two doses of xanomeline or placebo
  - Applied using a transdermal patch
  - 254 patients with mild to moderate Alzheimer's disease
  - Change from baseline in Week 24 Alzheimer's disease assessment scale - cognitive subscale of 11 items

Alzheimer's Disease Assessment Scale

Cognitive Subscale

- 11 Items
  - Word Recall Task
  - Naming Objects and Fingers
  - Following Commands
  - Constructional Praxis
  - Ideational Praxis
  - Orientation
  - Word Recognition Task
  - Remembering Test Directions
  - Spoken Language
  - Comprehension
  - Word-Finding Difficulty
- Range 0-70

- Interpretation
  - Score of 0-8 suggests normal cognition.
  - Scores of 9-18 indicate mild cognitive impairment.
  - Scores of 19-29 suggest moderate cognitive impairment.
  - Scores of 30 or higher suggest severe cognitive impairment.

Thanks

Richard C. Zink, PhD
Principal Research Fellow
JMP Statistical Discovery LLC

Adjunct Professor
Department of Biostatistics
University of North Carolina at Chapel Hill
richard.zink@jmp.com