Global Drug Development
Analytics

Post-baseline subgroups

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Overview

- Post-baseline subgroups: What's the issue?
- Are questions related to post-baseline subgroups relevant?
- How to approach these questions?

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Post-baseline subgroups: What's the issue?

Analysis and Interpretation of Treatment Effects in Subgroups of Patients in Randomized Clinical Trials

Salim Yusuf, DPhil, MRCP; Janet Wittes, PhD; Jeffrey Probstfield, MD; et al

JAMA. 1991;266(1):93-98. doi:10.1001/jama.1991.03470010097038

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Yusuf et al. (1991): Proper subgroup

“... We define a proper subgroup as a group of patients characterized by a common set of "baseline" parameters. These parameters may include inherent patient characteristics that cannot be affected by treatment (eg, age, sex) or disease characteristics defined before randomization. ...”

“... An improper subgroup is defined herein as a group of patients characterized by a variable measured after randomization and potentially affected by treatment. ...”

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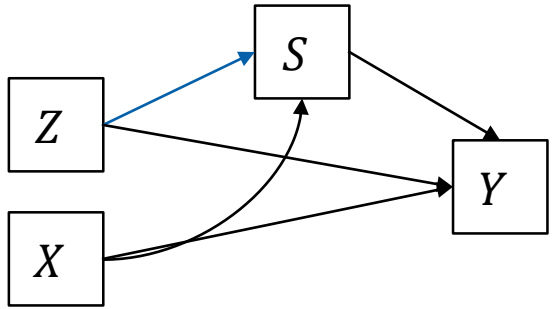
What's the issue?

- Y – outcome (e.g. measured at week 12)
- S – (postbaseline) subgroup indicator
- Z – treatment
- X – baseline characteristics



- Variable S may be affected by Z
  - Patient population with $S = 1$ on treatment arm ($S(1) = 1$) and control arm ($S(0) = 1$) may be systematically different
  - Naive comparison of Y is not comparing "like with like"
  - Observed effect may be due to treatment or the difference in baseline characteristics

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Are questions related to post-baseline subgroups relevant?

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials

Subgroup Variable (S): Treatment discontinuation due to Adverse Event

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The Combination of Exposure-Response and Case-Control Analyses in Regulatory Decision Making

The Journal of Clinical Pharmacology
53(2) 160–166
©The Author(s) 2012
DOI: 10.1177/0091270012445206

Abstract

To reduce the bias introduced by confounding risk factors, a case-control comparison was incorporated in the exposure-response (ER) analysis to evaluate the recommended dosing regimen for trastuzumab in a pivotal trial. Results of Kaplan-Meier survival analysis suggest that patients with metastatic gastric cancer (mGC) in the lowest quartile trough concentrations of trastuzumab in cycle 1 ($C_{min,1}$) had shorter overall survival (OS) than did those in other quartiles. The result of the case-matched control comparison suggests that adjusting for these risk factors, patients with the lowest quartile of trastuzumab exposure did not benefit from addition of trastuzumab treatment to chemotherapy. The identified subgroup without survival benefit and the ER relationship support the recommendation on conducting clinical trials to identify a treatment regimen with greater exposure and acceptable safety profiles and to prospectively evaluate whether this treatment regimen will result in survival benefit for the identified subgroup.

Subgroup Variable (S): Low plasma drug concentration after cycle 1

Evaluation of atezolizumab immunogenicity: Efficacy and safety (Part 2)

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Abstract

Antibody therapeutics can be associated with unwanted immune responses resulting in the development of anti-drug antibodies (ADA). Optimal methods to evaluate the potential effects of ADA on clinical outcomes in oncology are not well established. In this study, we assessed efficacy and safety, based on ADA status, in patients from over 10 clinical trials that evaluated the immune checkpoint inhibitor atezolizumab as a single agent or as combination therapy for several types of advanced cancers. ADA can only be observed post randomization, and imbalances in baseline prognostic factors can confound the interpretation of ADA impact. We applied methodology to account for the confounding effects

Subgroup Variable (S): Presence of anti-drug antibodies

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DOI: 10.1002/bimj.202000269

Biometrical Journal

RESEARCH ARTICLE

Efficient, doubly robust estimation of the effect of dose switching for switchers in a randomized clinical trial

Kelly Van Lancker[1] | An Vandebosch[2] | Stijn Vansteelandt[1,3]

Abstract

Motivated by a clinical trial conducted by Janssen Pharmaceutica in which a flexible dosing regimen is compared to placebo, we evaluate how switchers in the treatment arm (i.e., patients who were switched to the higher dose) would have fared had they been kept on the low dose. This is done in order to understand whether flexible dosing is potentially beneficial for them. Simply com-

Subgroup Variable (S): Switching to a higher dose of the treatment

Per-protocol-set analysis

- By far most common post-baseline subgroup analysis
- Why performed?
- ICH E9 (1998):

  "... The use of the per protocol set may maximise the opportunity for a new treatment to show additional efficacy in the analysis, and most closely reflects the scientific model underlying the protocol ..."

- Subgroup Variable (S): Adherence to the trial protocol

- Of particular interest in non-inferiority and bioequivalence trials
- Lou, Y., Jones, M. P., & Sun, W. (2019) propose a causal estimand & analysis strategy for bioequivalence setting
- Akacha, M., Bretz, F., & Ruberg, S. (2017) propose tripartite estimand

Summary

- Proper clinical/scientific interest
  - Analyses strategies sometimes improper
- Many “post-baseline” subgroup analyses related to
  - Assessment of consistency of overall treatment effects
  - Improvement of the treatment (e.g. the dose or administration frequency, etc)
  - Assessment of a more scientific/pure treatment effect

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How to approach these questions?

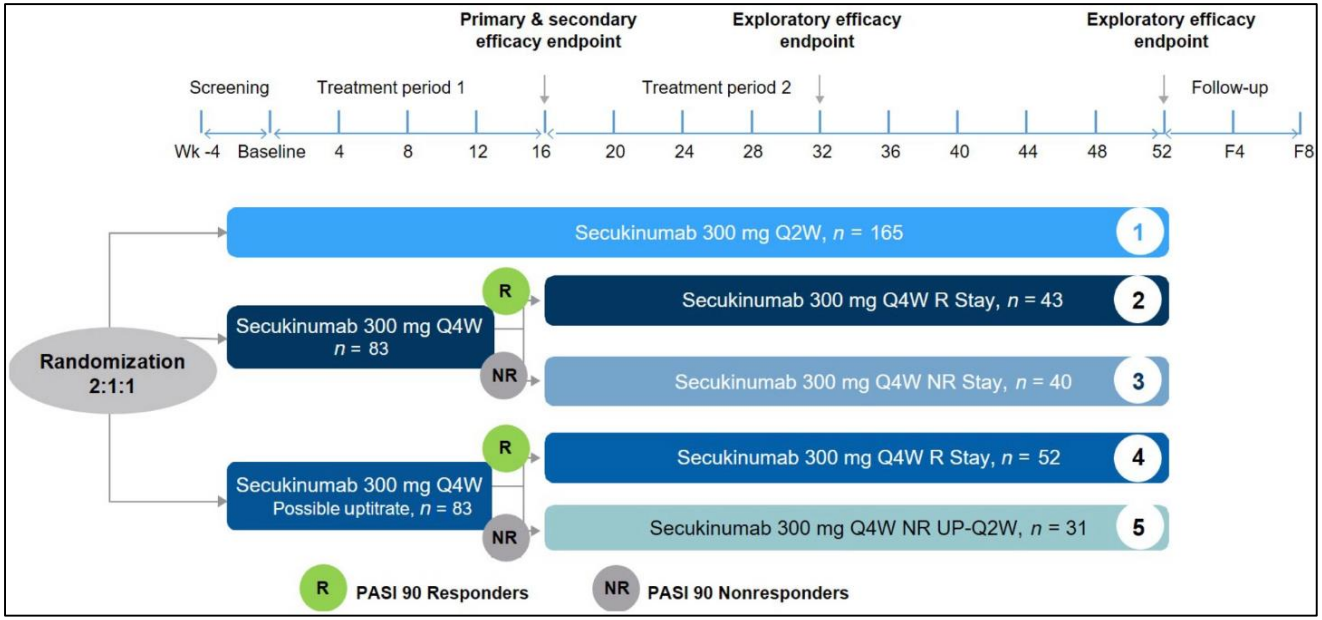
How to approach these questions?

- Need clear formulation of estimand
  - Need estimand to decide whether an analysis is proper or improper
  - Naive, improper subgroup analyses have no clear estimand
- ICH E9(R1) estimand thinking process (slightly adapted)
  - Trial objective/question
  - Estimand (target of estimation)
  - Trial design, data collection, estimation method
  - Assumptions, sensitivity analyses
  - Documentation

Clever designs reduce need for assumptions

- Features such as run-in phases or re-randomization can be used
- Example
  - Do treatment “non-responders” benefit from receiving an increased dose?
  - Can re-randomize non-responders after a specific time to get an increased dose or stay on the initially assigned dose

Clever designs reduce need for assumptions



Augustin et al. (2022), British Journal of Dermatology

Design allowed to assess the benefit of uptitrating non-responders (comparison of group 3 and 5)

→ uptitration randomized

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Principal stratum strategy

- One of the intercurrent event strategies suggested in ICH E9(R1)
- Define subgroup defined in terms of *potential outcomes* $S(Z=0)$ and $S(Z=1)$
  - e.g. patients that would have $S=1$ if on treatment ($S(Z=1)=1$)
  - or patients that would have $S=1$ on both control and treatment ($S(Z=0)=1$ and $S(Z=1)=1$)
- Subsetting on the same group, compares "like with like" → causal effect
- Such defined subgroups are called principal strata (Frangakis & Rubin, 2002, see also Mealli & Mattei 2012)

Principal stratum strategy

- In practice only one of $S(Z=0)$ or $S(Z=1)$ is observed for a patient
- Estimand cannot directly be estimated
  - untestable assumptions are required for estimation
  - bounds can be identified (based on sensitivity pars.) → Chiba & Vanderweele (2011)
- Bornkamp et al (2021) discusses 5 situations where principal stratum estimands may be of interest
  - Also review different type of assumptions

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Alternatives to principal stratum estimands

- Stensrud & Dukes (2022) propose alternative questions and estimands that may be of interest for considered 5 situations
  - criticize principal stratum estimands, because
    - membership to a *basic* principal stratum is not observable
    - there is no randomized experiment that would allow direct estimation of this effect
- Proper subgroup analyses

$$E(Y(Z=1) - Y(Z=0)|X)$$

  - Conditional treatment effect depending on covariates X
  - If there is a function $\mu_Z(X)$ predicting the probability of $S(Z)=1$ can also utilize

$$E(Y(Z=1) - Y(Z=0)|\mu_Z(X) > c)$$

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Alternatives to principal stratum estimands

- Sequential trial estimand

$$E(Y(Z_1 = 1, Z_2 = 1)|S(Z_1) = 1)$$
$$-E(Y(Z_1 = 1, Z_2 = 0)|S(Z_1) = 1)$$

  - A re-randomization design allows estimation without strong assumptions
  - Without re-randomization untestable assumptions needed for estimation

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Alternatives to principal stratum estimands

- (Conditional) separable effects
  - Assume treatment Z can be separated into components relating to Y (Z_Y) and S (Z_S)

$$E(Y(Z_Y = 1, Z_S = z_s)) - E(Y(Z_Y = 0, Z_S = z_s))$$

  - Can also consider estimands in subgroups defined by $S(z_S) = 1$ → closely related to principal stratum estimands
  - Estimation very similar to mediation-type estimands
  - Estimation possible, when there are no causal paths from Z_Y to S and Z_S to Y & conditional independence assumptions related to possibly time-varying confounders

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Conclusions

- Questions related to post-baseline subgroups are common and of interest
- Recommend to follow the estimand thinking process to allow for clear formulation of question, target estimand, design, analysis and assumptions
- No free lunch! This requires
  - more thought about question/estimand/design/analysis (high risk of non-obvious traps and pitfalls)
  - potentially complex designs, analyses and sensitivity analyses
  - more effort in communicating (setup of design/analysis and results)
- ... but get more (and the relevant) information from the data

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