Subgroup or Principal Stratum Analysis? A Comparison and guidance for Use of the Principal Stratum Framework for COA Endpoints

Skaltsa K[1], Eusebi P[2] and Kral P[3]
[1]IQVIA, Barcelona, Spain; [2]IQVIA, Rome, Italy; [3]IQVIA, Bratislava, Slovakia

Introduction

- Often treatment effects in *subsets of patients* in a clinical trial are of interest, especially to clinicians. These subsets may be subgroups based on **baseline characteristics**, e.g., age groups, mutation status etc. or defined based on the **occurrence of a post-randomization event**, e.g.:

01

In patients who (would or would not) experience an ICE

- Survive/die
- Adhere to treatment
- Do not require treatment interruption or dose modifications
- Do not qualify for surgery/transplant

ICE: intercurrent event

02

In patients who (would) respond to treatment

- As per RECIST criteria in oncology
- As per ACR criteria in rheumatology
- Achieve certain biomarkers levels

ACR: American College of Rheumatology;
RECIST: Response Evaluation Criteria in Solid Tumors

- For events occurring post-randomization, it is common to estimate the treatment effects by selecting a subgroup of patients who experienced the event of interest in the trial and apply the same statistical method as for the full population. However, this provides a comparison that breaks randomization, which may be undesirable. The principal stratum framework is an appropriate statistical solution for such setting.
- In this poster, we will explain what a **principal stratum** is as per the ICH E9(R1) guideline[1], how it compares to a subgroup, the associated statistical methodology and when it could be appropriate for use. Resources on how to implement it are also provided.

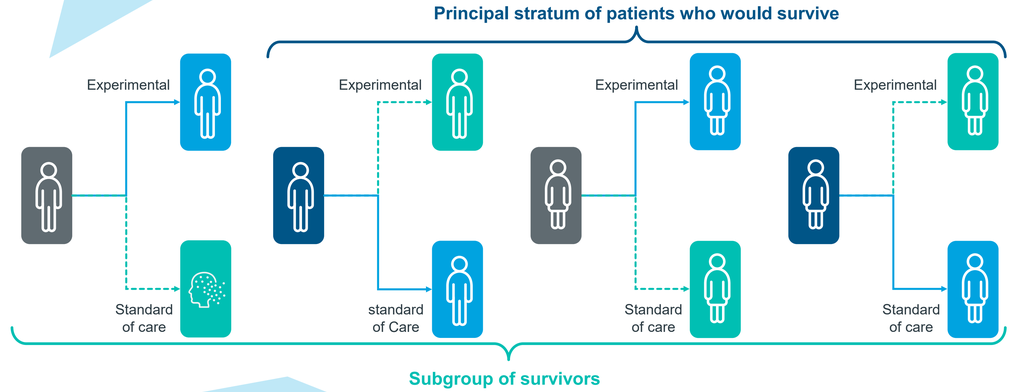
Discussion

- **Researchers are encouraged to utilize the principal stratum framework to estimate causal effects addressing *intercurrent events* or in populations defined based on the occurrence of *post-baseline events*, such as response, progression etc., which are frequent supplementary questions of interest to clinicians.**
- **The assumption of having collected all covariates predicting the occurrence of the events of interest is difficult to verify and needs to be kept in mind and communicated properly.**
- **If the number of patients who experienced the ICE is similar to the number of patients in the principal stratum, then the naïve sub-setting approach will provide similar results to the principal stratum approach. However, this can only be examined once the stratum membership has been predicted.**

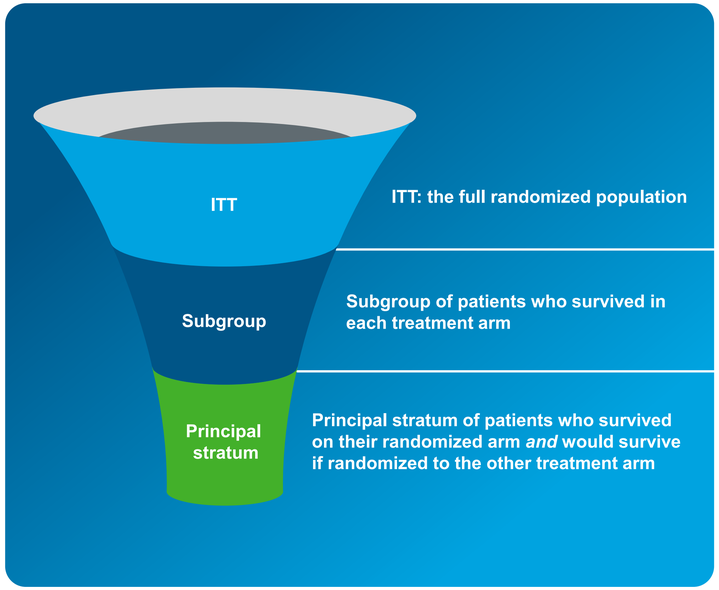
What is a principal stratum and how it differs from a subgroup?

First patient survived in the trial, but would not survive if he were randomized to the other treatment arm (according to a prognostic model)

The principal stratum of survivors consists of patients who would survive under either randomized arm



Survivors on the standard of care arm can arguably be considered *healthier/fitter* than survivors on the experimental arm as they receive benefit from a less effective drug



Illustrations using an example intercurrent event of death and a principal stratum of patients who would survive under either treatment arm

What are the steps to implement this strategy

Let's assume the ICE is **death** and the principal stratum of patients that ***would survive under any treatment*** is of interest. These are the 3 steps to follow to implement the principal stratum strategy. SAS macros to implement this approach can be found on the DIA WG on Estimands and Missing Data webpage[2].

Step 1

Predict if patients would die under the treatment arm they were not randomized to

I

- This can be achieved using a ***logistic regression or survival analysis*** borrowing information from the **observed survival status** of patients randomized to the other treatment arm, and use of **baseline covariates** considered as predictive of dying
  - This assumes all predictive covariates are collected
- Do this several times on multiple datasets (use Multiple Imputation (MI) framework)

Step 2

Select subset of patients who would survive under any treatment arm (principal stratum)

II

- If a patient survived during the clinical trial and their prediction "if randomized to the other arm" is also of survival, then this patient pertains to the principal stratum of patients who would survive under either treatment arm. We select patients that fulfill both conditions

Step 3

Estimate the treatment effect for each imputation and combine results

III

- Estimate the treatment effect using the appropriate estimator on each imputation dataset
- Treatment difference estimates are combined using Rubin's combination rules

[1] ICH E9(R1) Addendum on Statistical Principles in Clinical Trials;
[2] DIA website at: https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data

International Society for Quality of Life Research (ISOQoL) Annual Conference 2025, 22-25th October 2025, Milwaukee (WI), US