A practical guide to adding patient heterogeneity into Phase 3 trials: Case study in schizophrenia

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Summary & Key points

• An enrichment study was conducted to support relaxing eligibility criteria for Phase 3 trials in schizophrenia without increasing sample size, nor compromising detection of the new drug effect. Namely, the impact of the following trial design changes was assessed:
  – Relax a few, selected exclusion criteria in a controlled way
  – Quantify the gain in prediction accuracy of antipsychotic real-world effects (=effectiveness)
  – Measure probability of success of the new trial while keeping sample size constant

• Enriching typical Phase 3 trials with selected factors improved their generalizability and as a result, the predictions of the real-life effects of the investigated drug.

• The best choice of population enrichment factor to improve prediction of real-life effects was found to be driven by:
  – Size of the usually-excluded real-life population. Re-including patients with either a past suicide attempts or a disease chronicity between 1-3 years opened the trials to the largest real-world schizophrenia populations.
  – Change in outcome in patients with this factor. Patients with disease chronicity between 1-3 years, a BMI smaller than 17 or larger than 40, or being treated at a private practice only had the most different outcome (clinical symptoms) from typical Phase 3 patients.

• The probability of success of the corresponding Phase 3 trials enriched with the above real-life patients was improved.
Introduction

Phase 3 trials typically exclude patients with certain baseline characteristics, such as older age or co-morbidities, and thereby hamper learning of new drugs’ effectiveness in real-life. A population enrichment study was conducted to support implementation of new inclusion criteria for Phase 3 trials in schizophrenia without increasing sample size, nor compromising detection of the new drug effect.

Methods

A modeling & simulation study (“population enrichment study”) was performed using data from the observational SOHO cohort study including 10,281 schizophrenia patients, which was assumed to reflect the real-life schizophrenia population.

The impact on drugs outcome (symptoms evolution at 3 months) of re-introducing through stratification each of the following patient populations typically excluded from schizophrenia Phase 3 trials was explored: (1) age > 65 years, (2) disease chronicity between 1 and 3 years, (3) patients with one previous suicide attempt, (4) patients with a history of alcohol or substance abuse, (5) patients treated in private practices and (7) patients with a BMI < 17 or > 40. Patients with either one or two of these exclusion criteria replaced patients included in a Phase 3-like trial, until their real-life proportion in schizophrenia was reached. The real-life effect of the two most prevalent antipsychotic drugs (drugs A and B) was predicted using ordered probit regression models built only on data from each enriched Phase 3 population data, and compared with their actual real-life effect. The probability of success of the enriched trial comparing drug A and drug B was evaluated for different levels of enrichment.

Results

The effect of the two most prevalent antipsychotic drugs was found to be larger in real-life than in the Phase 3-like population. Prediction accuracy of the real-life effect based on Phase 3 population data was improved when the Phase 3 trial was enriched by partly relaxing specific eligibility criteria while keeping the number of patients constant. The enrichment of Phase 3 trials comparing the two most prevalent antipsychotics also improved their probability of success.

The impact of enrichment was not equal among the 7 tested eligibility criteria. For instance, introducing patients with disease duration between 1-3 years or one previous suicide attempt increased the most both prediction accuracy and probability of trial success. Inversely, introducing patients older than 65 years old or with extreme BMI only yielded minimal improvement. For each factor, the optimal enrichment proportion coincided with the percentage of this patient type in real-life. Moreover, relaxing two factors achieved better results than using the factor separately.