Sharing recruitment sites with a precision-medicine based study: What is the impact on your study?

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Introduction

Asthma is a heterogeneous disease with diverse etiological drivers. Precision medicine (PM) randomized controlled trials (RCT) aim to demonstrate differential clinical efficacy for specific endophenotypes. Such approaches rely on well-powered biomarker-defined subgroup analyses. To identify and enroll eligible patients in a PM-study, screening a large number of patients is required.

The objective of this work?

Assess the impact a PM-study could have towards all-comer studies due to actively reallocating patients into a PM-study at shared sites.

Explanation

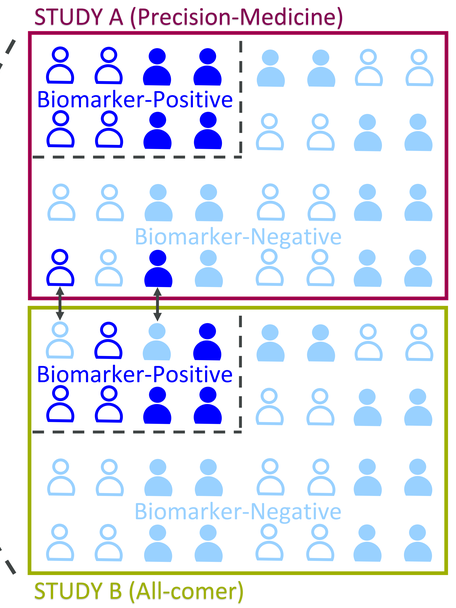
At a given site, patients could be randomized into two RCT:

- Study A, a precision-medicine-based RCT
- Study B, an all-comer RCT

Participants are recruited at sites which are running either study A (magenta), study B (lime-green) or both (magenta and lime-green).

Biomarker-Positive participants are preferentially recruited or actively reallocated into Study A thus changing the population-composition of Study B as this leads to fewer Biomarker-Positive patients recruited in the all-comer study.

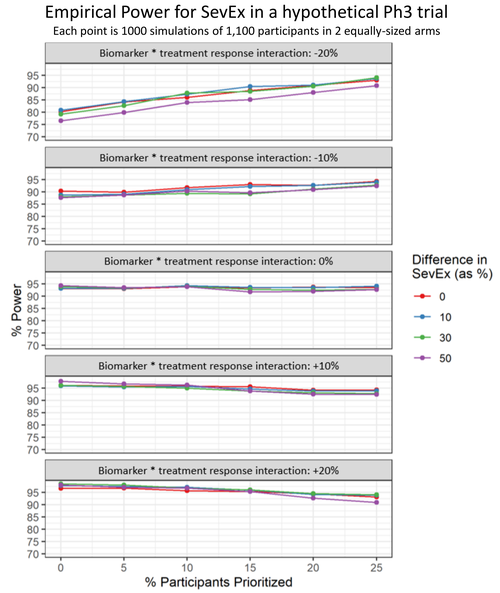
Methods



Biomarker-Positive Placebo Arm
Biomarker-Positive Treatment Arm
Biomarker-Negative Placebo Arm
Biomarker-Negative Treatment Arm

Modelling and simulations were used to approximate the impact of actively reallocating Biomarker-Positive patients into a PM-study. Both Forced Expiratory Volume (FEV1) and Severe Exacerbation rates (SevEx) were considered as endpoints and the impact on statistical power was quantified with respect to a hypothetical Phase 3 trial.

Results



In these analyses SevEx proved to be more sensitive to biomarker*treatment response interactions than FEV1 (data not shown).

Assuming a Phase 3 biomarker*treatment response interaction <10%, a Phase 3 trial could tolerate (i.e. <5% drop in power) up to a 15% loss of Biomarker-Positive patients.

A quantitative framework to see how all-comer studies may be affected by sharing sites with precision-medicine studies.

A modeling and simulation framework was designed to investigate site sharing. This framework can be used to assess how changes in the composition of subpopulations or subpopulation-specific perturbations influence the population as a whole. Assuming a Phase 3 biomarker*treatment response interaction <10%, a Phase 3 trial could tolerate up to a 15% loss of Biomarker-Positive patients.