PrecISE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

Methodological Challenges in PrecISE

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- PrecISE (Precision Interventions for SEvere asthma)
- Collaborative Studies Coordinating Center (CSCC) at the Department of Biostatistics UNC at Chapel Hill was awarded $61 million by the National Heart, Lung and Blood Institute in September 2017

NIH National Heart, Lung, and Blood Institute

NHLBI stated the following objectives for PrecISE

1. Run a controlled clinical trial **to evaluate efficacy** of several novel interventions in severe asthma patients
2. Use **precision medicine** approaches
3. Trial design needs to be **adaptive**

Precision medicine approaches in severe asthma

Several asthma treatment recently approved by the FDA:

Treatment	FDA approval	Approved for
FASENRA (benralizumab)	2017	Eosinophilic phenotype, blood eosinophils ≥300 cells/μl
DUPIXENT (dupilumab)	2018	Eosinophilic phenotype, blood eosinophils ≥300 cells/μl
Tezspire (tezepelumab)	2021	Unselected population, but better treatment effect was seen in patients with blood eosinophils ≥300 cells/μl

Interventions that are being evaluated in PrecISE in patients with severe asthma

- Imatinib (brand name Gleevec) is an oral chemotherapy to treat patients with cancer
- Clazakizumab, a novel therapy currently being investigated in psoriatic arthritis. Not yet approved for any indication
- Cavosonstat, a novel treatment, was investigated in cystic fibrosis but did not demonstrate benefit
- Broncho-Vaxom is known to support respiratory tract resistance to bacterial infections, has been used in Europe for the last two decades
- Medium chain triglycerides (MCT), a food supplement

Biomarker positive subgroups

Intervention	Subgroup	Prevalence
Imatinib	Eos < 300	62%
Clazakizumab	IL-6 > 3.1	33%
Cavosonstat	Genotypes	64%
Broncho-Vaxom	Eos ≥ 300	38%
MCT	FeNO ≥ 15 ppb	64%

Eos = blood eosinophils count

IL-6 = interleukin 6

FeNO = fractional exhaled nitric oxide

PrecISE is a multi-period crossover trial

Option 1: N of 1

Option 2: a sequence of 2-period crossovers

Option 3: one random placebo

16-week long periods with 4-week washouts

2 - 6 treatment periods for each participant depending on the time of entry to the study

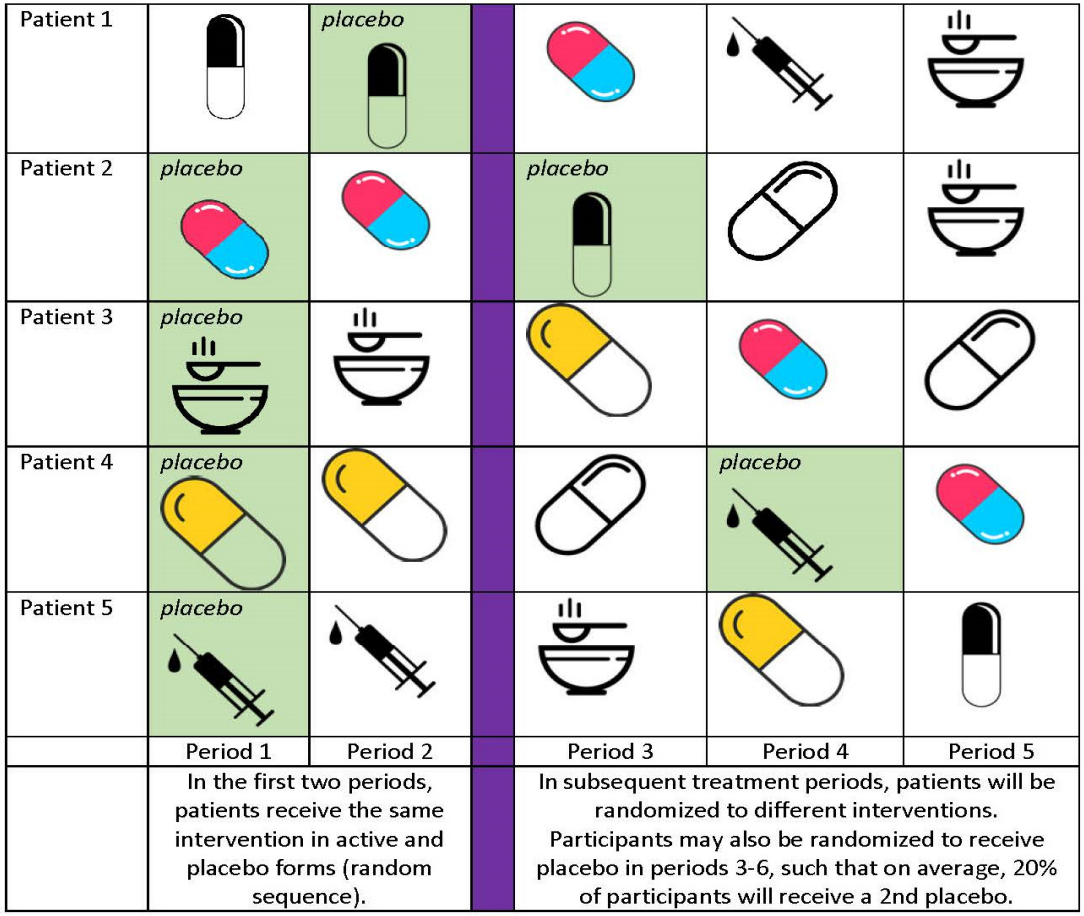
PrecISE is a multi-period crossover trial

Option 1: N of 1

Option 2: a sequence of 2-period crossovers

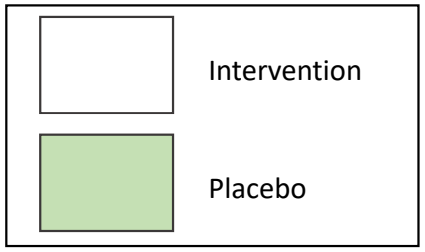
Option 3: one random placebo

PrecISE: 2-period crossover followed by a sequence of active treatments with possibly 1 more placebo



Other design decisions

- An inclusion of active control
  - Decided not to include
- Number of primary endpoints
  - 3
- Uncertainty about the value of within subject correlation
  - Interim analysis to estimate correlation



Study design in each arm

- Proportion of biomarker positive (A+) and negative participants (A-)
- Test in A+ only? in A-? in unselected?

Recent clinical trials in severe asthma

Treatment	Clinical Trials	Trial Design	Primary and Secondary Analysis
FASENRA (benralizumab)	CALIMA, SIROCCO	66% with blood eos ≥300*	Primary analysis in blood eos ≥300
DUPIXENT (dupilumab)	LIBERTY ASTHMA QUEST	44% with blood eos ≥300*	Primary analysis in unselected Prespecified subgroup analyses in blood eos ≥300
Tezspire (tezepelumab)	NAVIGATOR	50% with blood eos ≥300*	Primary analysis in unselected Prespecified subgroup analyses in blood eos ≥300

*Population prevalence of eosinophilic phenotype (blood eos ≥300) in severe asthma is 38%

How to design a trial with a biomarker defined subgroup?

- Phase 2 approach to designing a trial with a subgroup:
  - The goal is to show that the treatment effect is significantly different from 0 in a biomarker negative subgroup (**A-**) and/or a biomarker positive (**A+**)
  - The easiest is to run 2 parallel trials: in A- and A+
  - More efficient options are available (Freidlin et al., 2013; Parashar et al., 2016)

- Phase 3 approach to designing a trial with a subgroup:
  - The goal is to show that the treatment effect is significantly different from 0 in **unselected population** (A- and A+ combined) and/or in **A+**
  - The most efficient way is run a trial in A+ only
  - However, it is often desirable to enroll participants according to population prevalence (Rosenblum and Qian, 2016; Rosenblum et al., 2016, Dmitrienko et al., 2017)

Phase 2 versus phase 3 approach

- Phase 2 enrolls to A- and A+ according to the required allocation proportion
- Phase 3 enrolls according to the population prevalence

- Phase 3 approach requires 20-50% less participants
  - even more participants need to be screened to find the required number of A- and A+ participants

- When A+ prevalence is high, Phase 3 approach is likely to conclude that the treatment is effective in unselected population when only A+ shows activity (Rothmann et al., 2012)

Approaches we considered to design PrecISE

- Enroll A+ only
  - Advantage: will be able to utilize study resources in the most efficient way
  - Disadvantage: This design is not responsive to the Request for Application (RFA) since there is no precision medicine component

- Enroll A- and A+ according to the population prevalence and test for treatment effect in unselected and in A+ (Phase 3 approach)
  - Advantage: responsive to the RFA since we can update the biomarker cut-off during the trial (if we can halt enrollment to an intervention) or in a post-hoc analysis
  - Disadvantage: Not enough power for interventions with small subgroup

PrecISE Study Design

- Test for efficacy in A+ only
  - No testing for treatment effect in A- or in unselected population
- Enroll more participants from A+ than A-, 2:1 ratio A+/A-, this is to update the biomarker cut-off (precision medicine component)
  - If the biomarker cut-off is re-estimated during the trial, test for treatment effect in the combined sample of old A+ (before cut-off re-estimation) and a new A+ (after cut-off re-estimation)
  - Imatinib, cavosonstat, and MCT have subgroup prevalence of 64%, enrolling according to population prevalence (as in LIBERTY ASTHMA QUEST trial)
  - Clazakizumab and Broncho-Vaxom have subgroup prevalence of 38% and 33%, need to oversampe A+ (as in CALIMA and SIROCCO trials)

How to define the best subgroup?

- Definition 1. The best subgroup is defined as the largest subgroup with a treatment effect of at least Δ

- Definition 2. The best subgroup is defined as the subgroup maximizing

$$U = \text{Treatment effect} \times \text{Prevalence}^{\gamma}$$

When $\gamma = 0$, the treatment effect is maximized

When $\gamma = 0.5$, the power is maximized

- In PrecISE, we use $\gamma = 0.5$ due to the new cut-off being applied prospectively to baseline data of participants already on the treatment

How to update the cut-off at the interim and final analysis?

When updating a cut-off of a single biomarker, a non-parametric approach performed the best (Joshi et al., 2019)

Non-parametric approach : select the subgroup that maximizes

$$U = \text{Treatment effect} \times \text{Prevalence}^{\gamma}$$

When $\gamma = 0.5$, select the subgroup with the largest test statistic

How to adjust for multiplicity in post-hoc subgroup analysis?

- Cross-validation and bootstrap (Simon, 2008; Zhang, et al., 2017)
- Bootstrap (Guo et al., 2020)

PrecISE

- First participant screened Dec 2019
- First participants randomized Aug 2020
- 136 participants have been randomized as of April 1, 2022
- Target sample size 500

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