UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

Trial design considerations in the face of overdispersion and time-varying event rates

: a meta-regression approach with an application in asthma.

Bohua Chen

Christian Röver, Stefan Andreas, Christian Taube, Tim Friede

Department of Medical Statistics
University Medical Center Göttingen

Sample size: negative binomial

Negative binomial regression is commonly used in clinical trials with count endpoints.

λ_1: control rate; λ_2: treatment rate; φ: overdispersion parameter.

$\delta_1 = \log(\lambda_1/\lambda_2)$; $\theta = (\lambda_1, \varphi)$.

n: treatment-group size; rn: control-group size; d: common follow-up.

Sample size formula:

$$n_{\mathrm{NB}}(\theta) = \left\lceil \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{\delta_1^2} \left\{ \frac{1}{r} \left(\frac{1}{d\lambda_1} + \varphi \right) + \left(\frac{1}{d\lambda_2} + \varphi \right) \right\} \right\rceil .$$

Normal-approximation planning formula. Target power $1 - \beta$, two-sided level α; $\lambda_2 = \lambda_1 \exp\{-\delta_1\}$.

Historical evidence and future-trial prediction

62 asthma trials

Two separate classifications

Placebo type

Defined by allowed co-medication

- True (27)
- ICS (16)
- ICS–LABA (19)

Asthma severity

- Mild (16)
- Moderate (32)
- Severe (14)

Four reporting formats: likelihoods

Data	Model given λ_i, φ_i
I. Rate + SE	$\log R_i \sim \mathcal{N}(\log \lambda_i, s_i^2)$
II. Total count	$T_i \dot{\sim} \mathcal{N}(n_i\mu_i,\ n_i\mu_i(1+\varphi_i\mu_i))$
III. Event-free	$Z_i \sim \text{Binomial}(n_i, \pi_{0i})$
IV. Both	$p(T_i, Z_i) = p(Z_i)\, p(T_i \mid Z_i)$ $T_i \mid Z_i \dot{\sim} \mathcal{N}(k_i m_i^+, k_i v_i^+)$

$\mu_i = d_i\lambda_i$, $\pi_{0i} = (1+\varphi_i\mu_i)^{-1/\varphi_i}$, $k_i = n_i - Z_i$.
$m_i^+ = E(X_i \mid X_i > 0)$, $v_i^+ = \text{Var}(X_i \mid X_i > 0)$.
X_i: individual NB count; n_i: patients; d_i: follow-up.
s_i: SE of log rate; $\dot{\sim}$: normal approximation (II and IV).

Future-trial prediction: $\log \lambda_1 = \mathbf{x}^\top \beta + u_\lambda, \quad \log \varphi = \mu_\varphi + u_\varphi.$
$u_\lambda \sim \mathcal{N}(0, \sigma_\lambda^2)$, $u_\varphi \sim \mathcal{N}(0, \sigma_\varphi^2)$; $\mathbf{x}$: year and placebo type or severity.
Predictive draws include parameter uncertainty and future study effects.

ICS: inhaled corticosteroids; LABA: long-acting beta agonist; FEV_1: forced expiratory volume in 1 s.
Manuscript: Sec. 2.3, Appendix A and Table E1. Röver et al. (2016), doi:10.1002/bimj.201300288.

Three ways to determine the sample size

Fix δ_1, $\mathbf{x}$ and target power $1 - \beta = 0.80$.
Use the posterior predictive planning distribution $p(\theta \mid \mathbf{x}, D)$.

1. Plug-in estimate

Plug the posterior predictive medians into the sample size formula.

$$n_{\text{med}} = n_{\text{NB}}(\widetilde{\theta}), \qquad \widetilde{\theta} = \big(\text{med}(\lambda_1 \mid \mathbf{x}, D), \text{med}(\varphi \mid \mathbf{x}, D)\big)^\top.$$

2. Based on assurance

Choose the smallest n such that assurance (expected power) is at least 80%.

$$n_{\text{A}} = \min\left\{ n \in \mathbb{N} : \int \pi(n; \delta_1, \theta, \mathbf{x})\, p(\theta \mid \mathbf{x}, D)\, \mathrm{d}\theta \geq 0.80 \right\}.$$

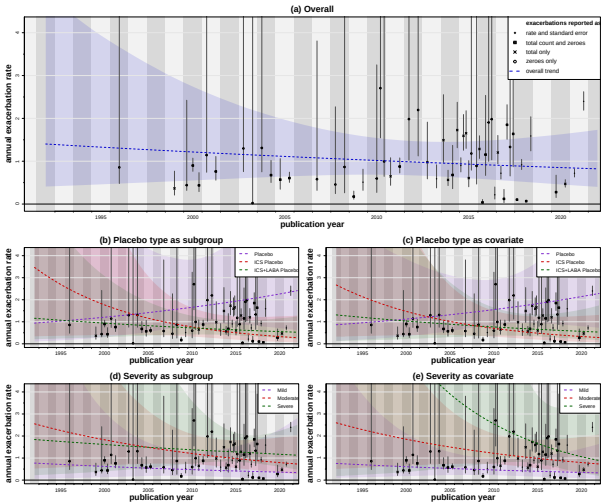
3. Posterior sample size

Derive the sample size distribution from joint predictive draws of (λ_1, φ); take the 90th percentile.

$$n_{0.90} = Q_{0.90}[n_{\text{NB}}(\theta) \mid \mathbf{x}, D].$$

D: historical data; π: conditional Wald power; $Q_{0.90}$: 90th percentile. Poisson versions set $\varphi = 0$.

Calendar time and population



Overall annual change

-1.8%

95% CrI: -7.5% to $+4.3\%$

Temporal trends remain uncertain.

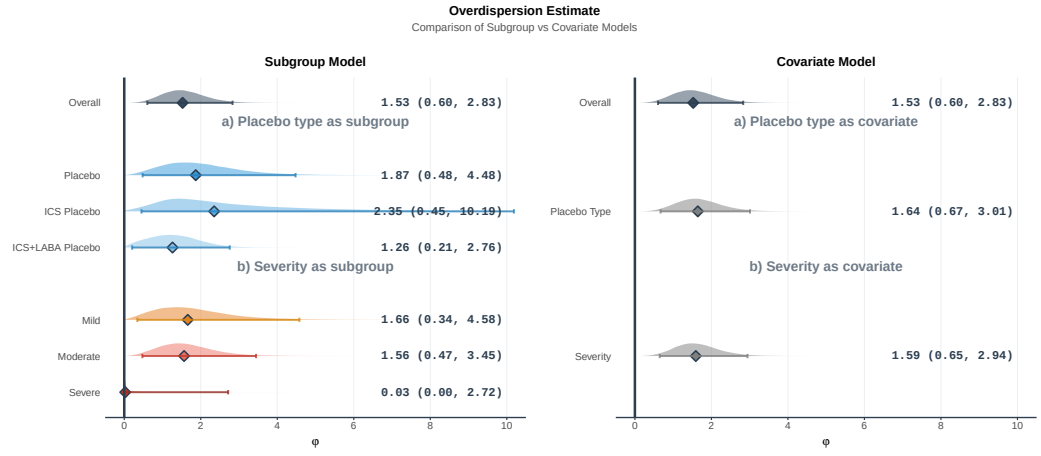
Plan for the target trial

Consider its calendar period, asthma severity and background therapy.

Subgroup and covariate models provide complementary estimates.

Annual exacerbation rates by publication year; manuscript Figure 1.

Three ways to joint analysis of all studies



Overall: $\exp(\mu_\varphi) = 1.53$ **(95% CrI: 0.60, 2.83).**

The near-zero estimate for severe asthma remains imprecise.

Subgroup-specific estimates and common estimates from covariate models.

Sample size implications in asthma

Planning inputs	λ_1 **(events/year)**	φ
NAVIGATOR protocol assumptions	0.900	$1/2.4 \approx 0.417$
Historical plug-in (2017; overall)	$\approx 0.894^*$	1.526

Similar event rate, but about $3.7\times$ the protocol overdispersion.

Rate ratio 0.5; $d = 1$ year; $r = 1$; two-sided $\alpha = 0.05$; target power 0.80.

Rule using historical predictions	**Per arm** n	**Total** N
Negative binomial: median plug-in	105	210
Negative binomial: 80% assurance	210	420
Negative binomial: predictive 90th percentile	585	1170

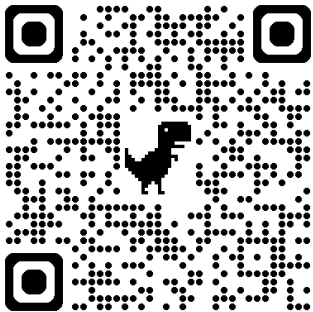
$^*\lambda_1 \approx \exp\{0.194 - 0.018 \times 17\} = 0.894$: reconstructed from rounded Table 3 coefficients; rate per patient-year.
Assurance and percentile rules use the joint predictive distribution.
Overall historical illustration; NAVIGATOR's population and design targets differ (Sec. 2.1).

Summary: plan for the future trial

- **Calendar time:** no clear evidence of a temporal trend in asthma exacerbation rates.
- **Target population:** align assumptions with asthma severity and background therapy.
- **Variability:** include overdispersion and between-trial heterogeneity.
- **Design and uncertainty:** specify the effect, follow-up, allocation and how predictive uncertainty enters the sample-size rule.

Use a predictive distribution tailored to the future trial.

Thank you for your attention!



Scan for the pre-print!
https://arxiv.org/abs/2610.21432

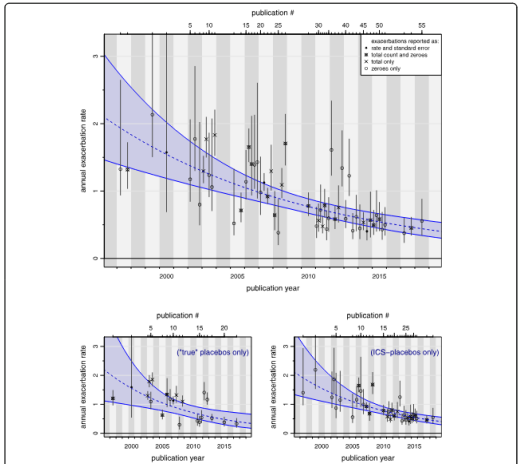


Fig. 2 Time trend in annualized exacerbation rates based on the Bayesian regression analysis (without adjustment for study or baseline characteristics). The dashed line shows the estimated rate over time along with a 95% credible region. The points and vertical whiskers indicate each individual study's estimated rate along with a 95% credible interval. The shown ("shrinkage") estimates are based not only on the corresponding study's provided data (which in some cases may not be sufficient to derive a rate estimate), but these are supported by the complete data set. Different types of data sources are indicated by different symbols (some references directly provide rate estimates along with standard errors, some report the total number of exacerbations and the number of exacerbation-free patients, and some only one of the two). Within each publication year, estimates are evenly distributed so that they are identifiable by their respective index (see axis at top and Additional file 1: Table S1). Inserted below are two smaller figures illustrating the time trend for the two subsets of "true" placebos (21 studies) and ICS-placebos (34 studies)

Figure: Motivation example of COPD case (Andreas et al., 2019)