Estimands for the percent change from baseline: Guidance for clinical trials

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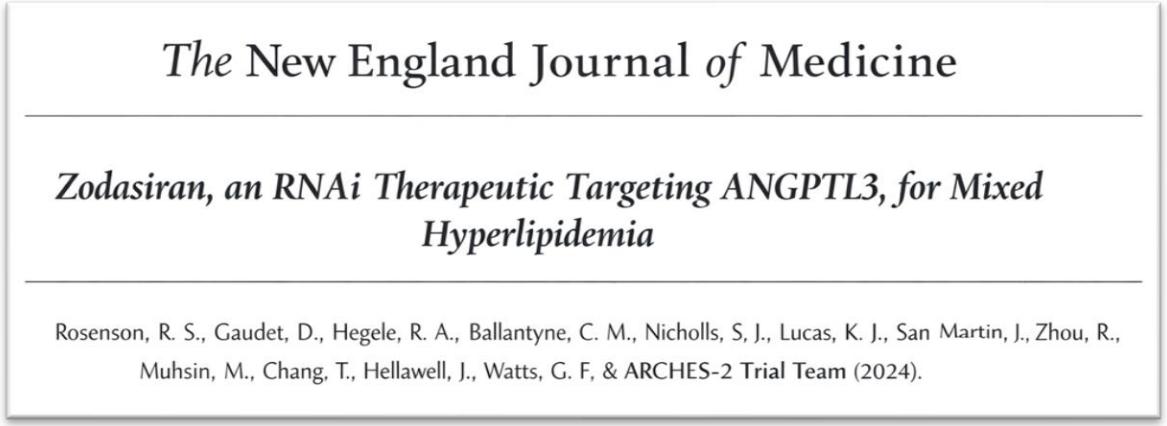
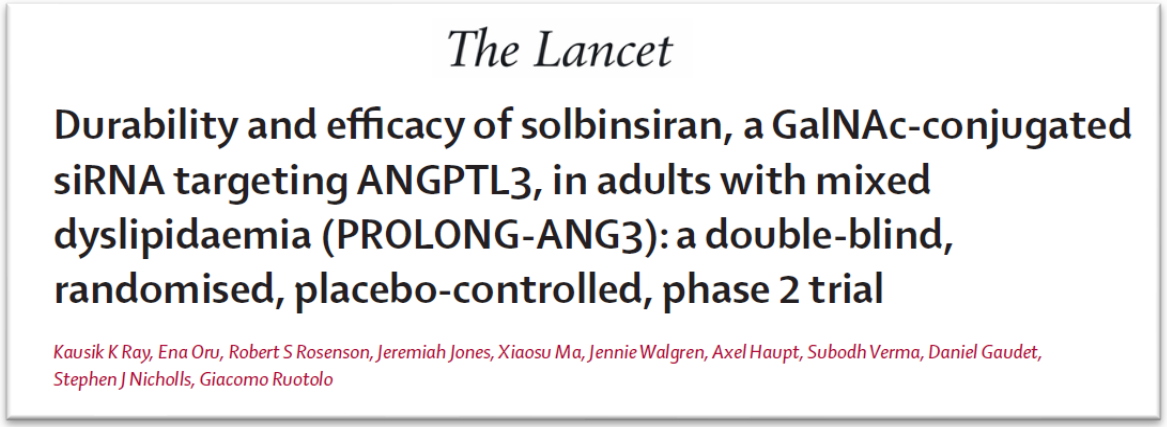
A motivating example

Two recent publications from molecules in the lipid lowering space

- Phase 2 trials for siRNA therapies with **similar indications, patient populations and study designs**
- Primary endpoints differ (apoB vs. triglycerides) but **large overlap in lipids** across primary / secondaries.
- Endpoints specified as **"percent change from baseline"** in both publications (Day 180 vs. Week 24)
- Data analysis by linear mixed model in both trials.





Comparing the reporting language for treatment effect estimates across trials (taking triglycerides as an example)

Rosenson et al (2024)

"The difference in change from baseline as compared with placebo was −51 percentage points."

Ray et al (2025)

"The placebo-adjusted percent change from baseline was –36·3%."

- What was the estimand of the trial?
- Specifically, are comparisons of −51 against –36·3% valid?
- Language suggestive of the same estimand being used however, in Ray et al (2025):

"All lipid-related parameters […] were log-transformed before the analysis […]."

A straight-forward approach: modelling the percent change from baseline

Y_0: Baseline value

Y_1: Post-treatment value

Trt: Treatment indicator

- Approach of Rosenson et al (2024) is*:

$$100\% \times (Y_1/Y_0 - 1) \sim N(\alpha_0 + \alpha_1 Y_0 + \alpha_2 Trt, \sigma^2).$$

* Simplified to single timepoint

- Targets the **expected percent change from baseline**,

$$100\% \times (E(Y_1/Y_0) - 1),$$

and the between-group **difference in expected percent change from baseline**, α_2.

- Distribution of response variable asymmetric and bounded at –100%.
- Potential for heteroskedastic variance, especially for substantial inhibitory effects.

To log or not to log.
What's the difference anyway?

- Log-normal models are often suitable for laboratory values, e.g. lipid concentrations.
- Ray et al (2025) model the **log ratio to baseline**:

$$\log(Y_1/Y_0) \sim N(\beta_0 + \beta_1 \log(Y_0) + \beta_2\, Trt, \sigma^2)$$

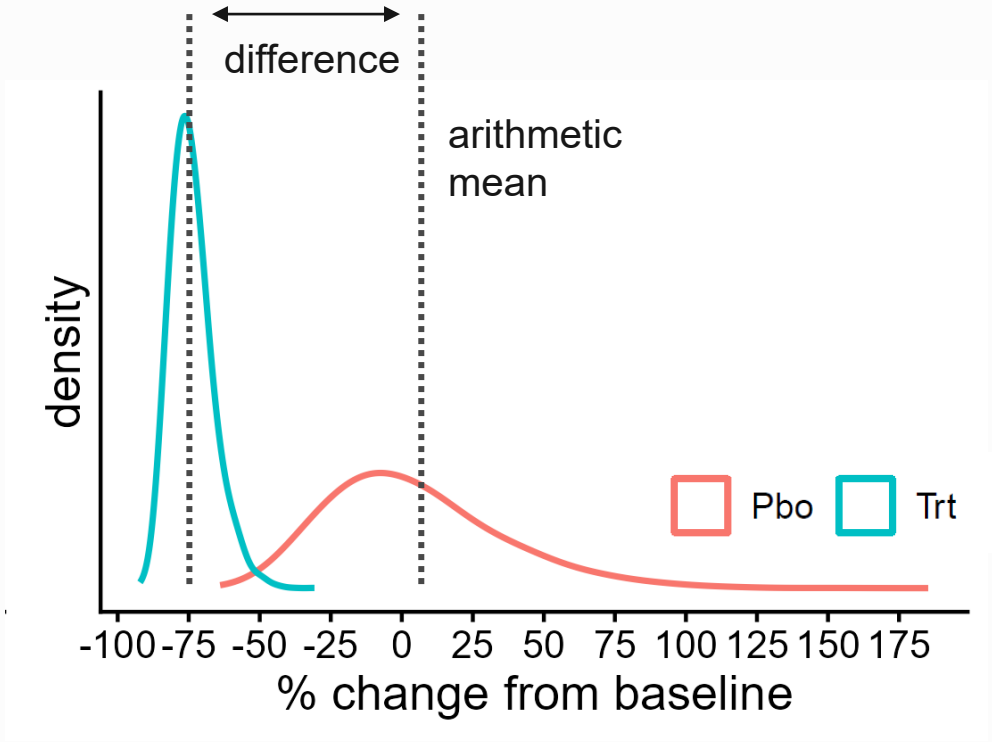
- Treatment effect β_2 is transformed into a percent change using $100\% \times (\exp(\beta_2) - 1)$.
- **However:** by Jensen's inequality, $\exp(E[\log(Y_1/Y_0)]) \neq E[Y_1/Y_0]$.
- This estimator targets a different estimand: the **expected geometric mean ratio to baseline**,

$$\exp(E[\log(Y_1/Y_0)])\,,$$

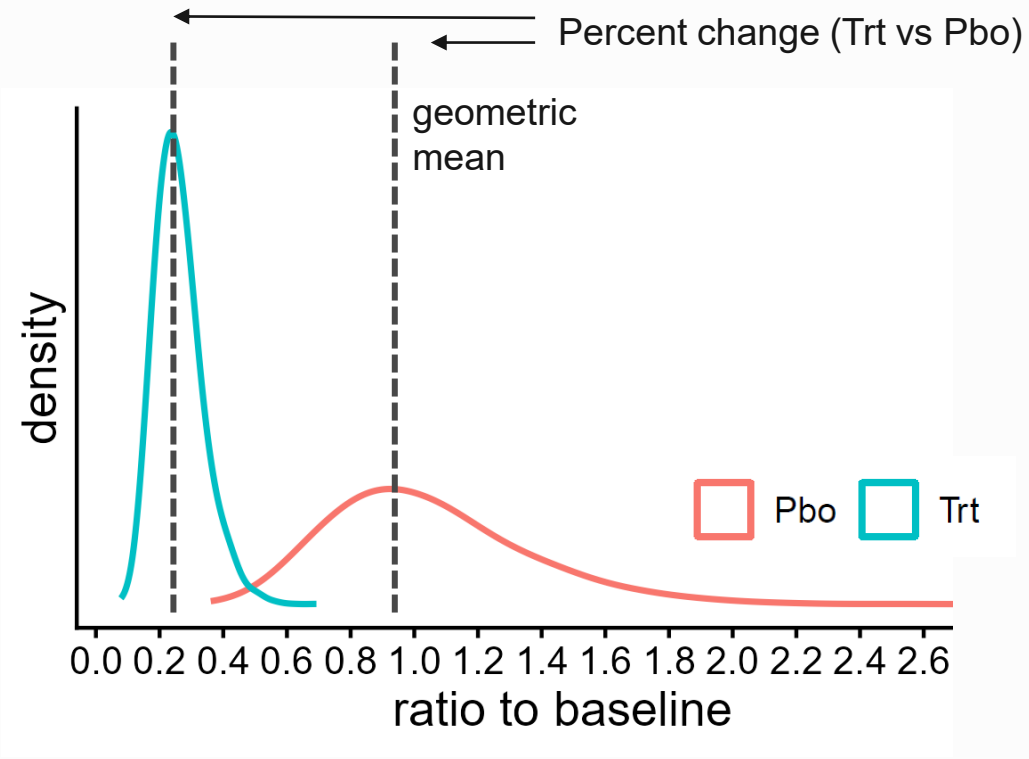
  and their percent change between groups.

Toy example to illustrate the difference between the two estimand summary measures

Model of % change from baseline



Model of log ratio to baseline



A guide to accurate reporting language for estimands of the log ratio model

Another look at Ray et al (2025)

Endpoint:

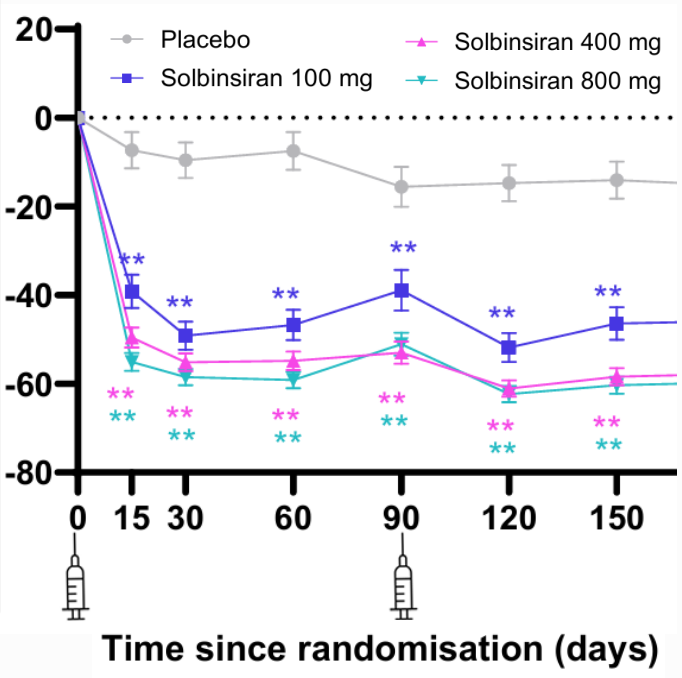
The percent change from baseline

The ratio to baseline

Within-group summary measure:

Geometric mean ratio to baseline

Percent change from baseline (%)



Between-group summary measure:

The placebo-adjusted percent change from baseline was –36·3%.

The percent change in geometric mean ratios to baseline between active and placebo groups was -36·3%.

???

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Getting the best of both worlds:
Intuitive interpretation with appropriate distributional assumptions

For log-normal data, can recover the difference in mean percent change from log ratio model:

- If $log(X) \sim N(\mu, \sigma^2)$, then $E[X] = \exp(\mu + \frac{1}{2}\sigma^2)$.
- Use relationship to estimate $E[Y_1/Y_0]$ from model of $E[\log(Y_1/Y_0)]$.

Treatment effect estimate:

$$100\% \times \left[\frac{1}{n}\sum_i \exp\left(\hat{\mu}_{iT} + \frac{1}{2}\hat{\sigma}^2\right) - \frac{1}{n}\sum_i \exp\left(\hat{\mu}_{iC} + \frac{1}{2}\hat{\sigma}^2\right)\right]$$

n: total trial size
$\hat{\mu}_{ik}$: model prediction for patient i under treatment k

- Wrinkle: SEs and confidence intervals require e.g. bootstrapping or multivariate δ-method.
- For Bayesians using MCMC sampling, uncertainty quantification comes "for free".

R package coming!

Key take-aways

"Percent change from baseline" endpoints are common in clinical trials

- Analysis approaches vary and it's not always clear what was done.
- Results are easily misinterpreted by non-statistical audiences.

- Logarithmic transformations reflect a distinctly different estimand compared with direct estimation.
- Can target the difference in mean percent change from baseline using a log ratio model.

Accurate reporting language is critical: ensures treatment benefits are clearly communicated to the scientific community.

We propose a guide to accurate language for estimand attributes of the log ratio to baseline model.

Q&A

References

- Ray, K.K., Oru, E., Rosenson, R.S., Jones, J., Ma, X., Walgren, J., Haupt, A., Verma, S., Gaudet, D., Nicholls, S.J. and Ruotolo, G., 2025. Durability and efficacy of solbinsiran, a GalNAc-conjugated siRNA targeting ANGPTL3, in adults with mixed dyslipidaemia (PROLONG-ANG3): a double-blind, randomised, placebo-controlled, phase 2 trial. *The Lancet*. 405(10489), 1594-1607.
- Rosenson, R. S., Gaudet, D., Hegele, R. A., Ballantyne, C. M., Nicholls, S. J., Lucas, K. J., San Martin, J., Zhou, R., Muhsin, M., Chang, T., Hellawell, J., Watts, G. F., & ARCHES-2 Trial Team (2024). Zodasiran, an RNAi Therapeutic Targeting ANGPTL3, for Mixed Hyperlipidemia. *The New England Journal of Medicine*, *391*(10), 913–925.