SIMULATIONS Statistical Analysis

Using a **time-varying covariate** in the Cox proportional hazards model discerns early/late treatment efficacy. **Use with caution**.

Use of time-varying covariate in assessing disease remission in the early and late phases of treatment with application to RITAZAREM trial.

Marianna Nodale, Simon Bond

Cambridge Clinical Trials Unit

TRIAL BACKGROUND

RITAZAREM, an open-label, multi-centre RCT, aims to assess the efficacy of rituximab compared to the current standard of care in the prevention of relapse in ANCA-associated vasculitis.

Design: N = 170 patients, 1:1, 90% power at α = 5% for HR = 0.42.

Outcome: time to disease relapse.

Primary analysis: Cox proportional hazard model for overall efficacy

Clinical question: does treatment effect *persist* after the patient stops taking the drug?

Statistical analysis: Cox proportional hazard model with treatment interaction which includes a time-varying covariate to investigate early/late treatment effect.

$$\mathbf{I} \quad (\text{time} \leq \text{stop drug} = \tau)$$

Is the time-varying covariate model robust?

METHODOLOGY RESEARCH

1. Censoring and relapse times simulated with a Weibull distribution (sample N = 167, 83 events).
2. Relapse times after change point simulated with a conditional Weibull distribution.
3. Simulated $HR_{early} \neq HR_{late} \in (0.3, 0.9)$
4. True change point for HR τ = 20.
5. Analysis change point 10-30.

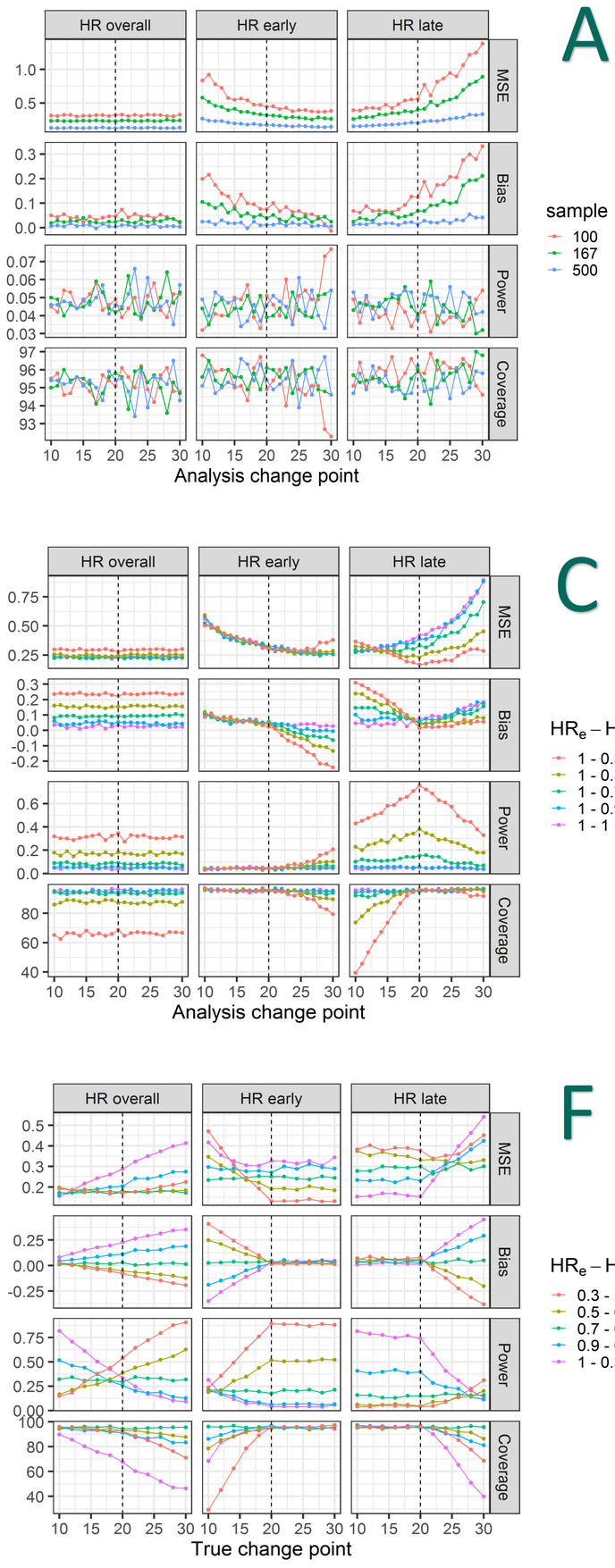
RESULTS

Simulations (n=1000) investigate the operational characteristics of the model under a variety of assumptions:

A. **Null hypothesis**
B. **Constant overall efficacy**
C. **Late efficacy**
D. **Early efficacy**
E. **Different early/late efficacy**
F. **Wrong change point τ**

DISCUSSION

- Null/constant efficacy ⇒ small sample size bias, controlled by increasing N.
- Different HR and mismatch between assumed/true τ ⇒ large bias, worsened by increasing N.



NIHR | National Institute for Health Research

UNIVERSITY OF CAMBRIDGE

Take a picture to download the **full paper**

SCAN ME

NHS Cambridge University Hospitals NHS Foundation Trust