Identifying optimal outcome measures for phase II trials in cancer

Sarah Brown

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Phase II outcome measures in cancer

- Drug development process assumes success at phase II allows to move to phase III with some degree of reliability
- Need to understand the relationship between the phase II and III outcomes
- Usually consider short term outcome measures that are, to some degree, ‘surrogates’ of overall survival e.g. overall response rate

- Specifically looking at advanced colorectal cancer (aCRC)
- Consider alternative phase II outcome measures to response
- Assume phase III outcome is overall survival (OS)

Outcome measures in aCRC

- Response, as measured by RECIST (CR + PR) – taken as reference outcome
- Non-progression (CR+PR+SD)
- Longitudinal tumour measurements as a continuous variable (SLD)
- Progression-free survival (PFS)

- Longitudinal tumour measurements and PFS assessed over whole time period, and also within 3 and 6 months, to reflect short-term outcomes used in phase II

Methods

- Use meta-analytic surrogacy methodology to quantify the relationship between phase II and III outcomes
  1. Trial level – assesses the ability of the treatment effect on the phase II outcome to predict the treatment effect on the phase III outcome – $\mathbf{R^2_{trial}}$
  2. Individual level – assesses the ability of the phase II outcome to predict the phase III outcome for an individual patient, after adjusting for treatment effects - $\mathbf{R^2_{indiv}}$

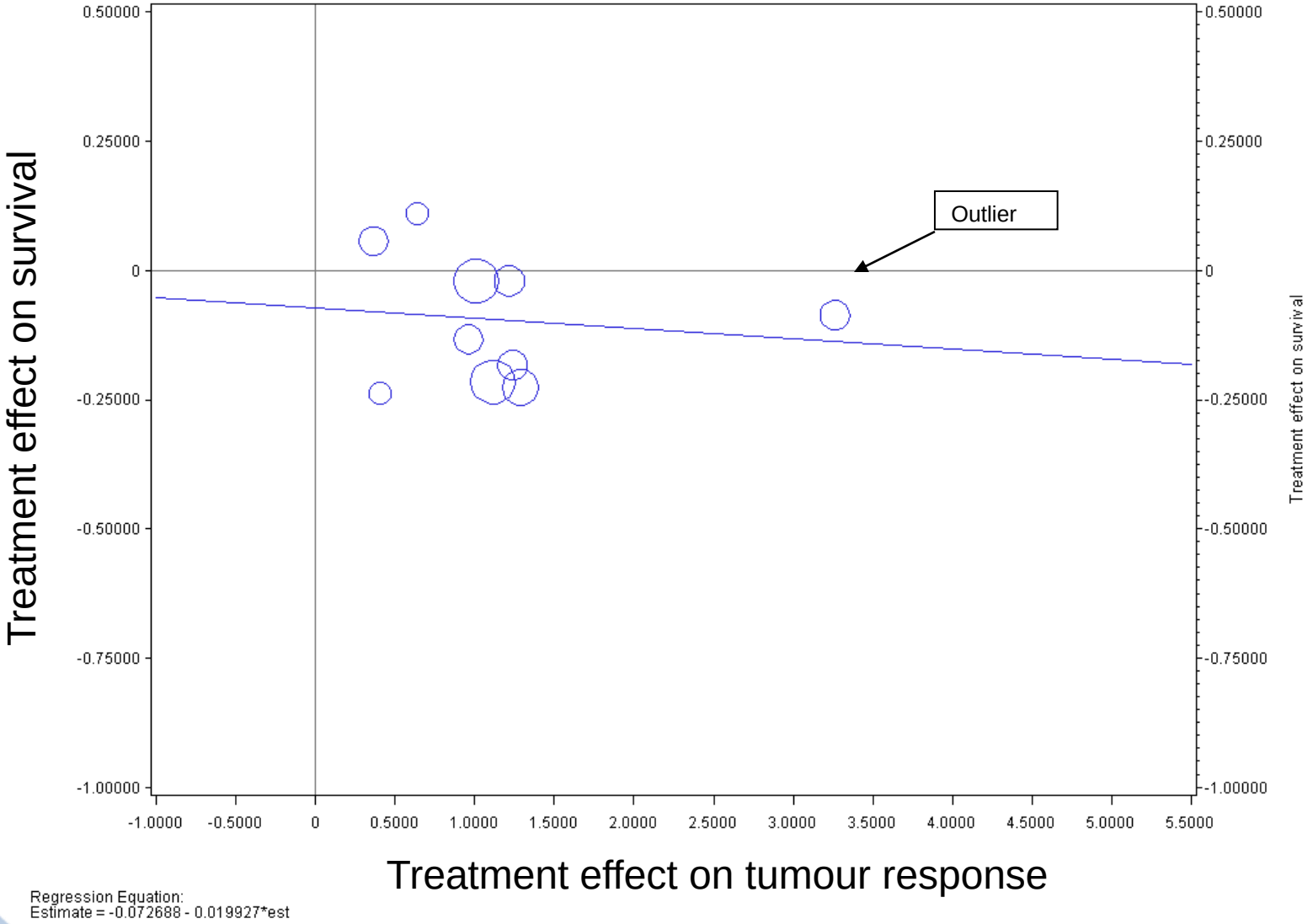
- Previously applied in phase III setting to **replace** outcome measures – require $R^2 = 1$
- In phase II setting, not looking to replace true, but to identify measures that reliably screen treatments for phase III

Data

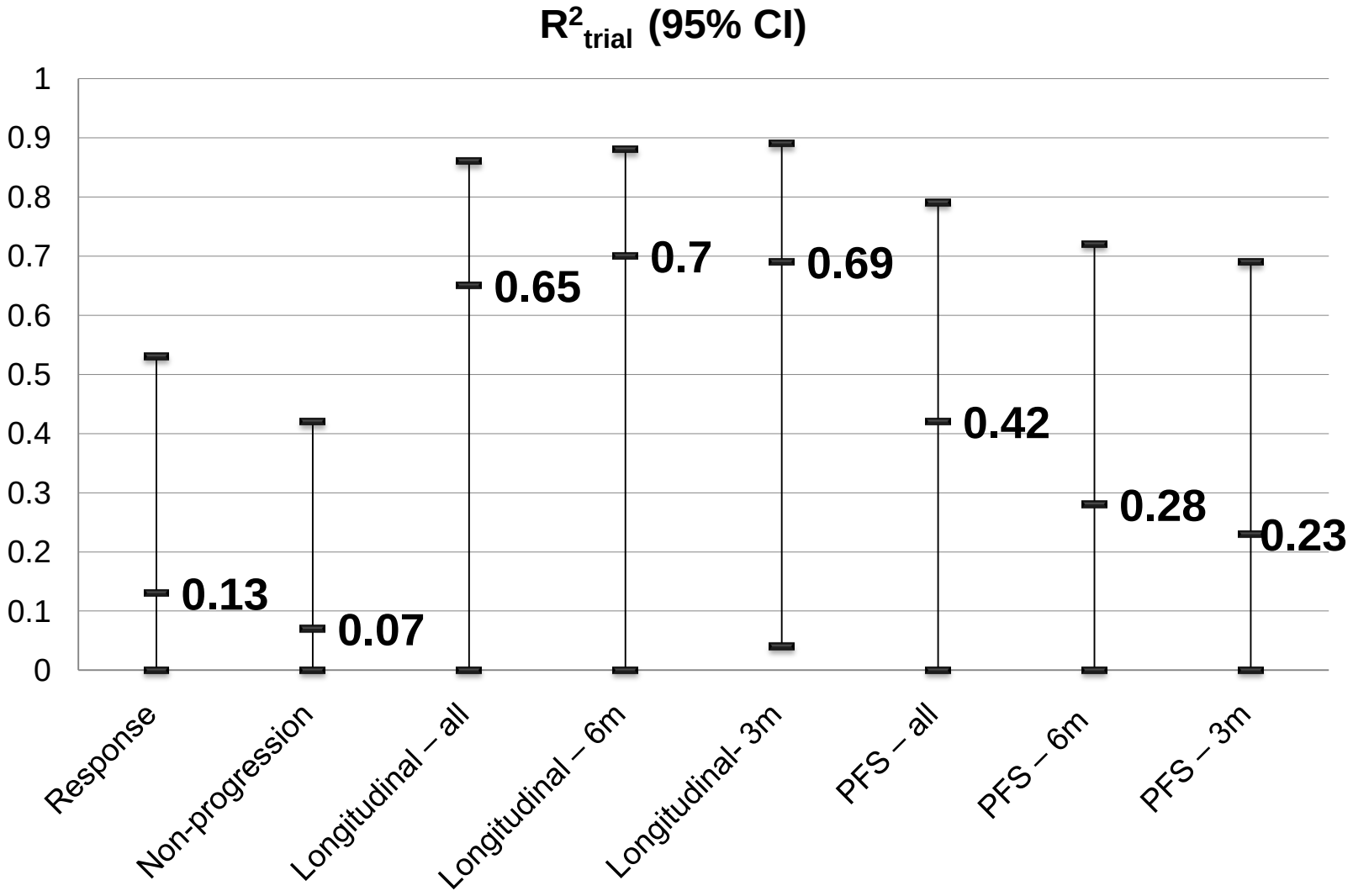
- Individual patient data from 7 clinical trials of aCRC, open to recruitment between 1999 and 2007
- 5435 patients
- 3-arm trials split => 10 grouping units
- Data collected on following: patient characteristics, date of tumour assessments, tumour size and tumour response at each assessment, date of progression, date of death / last date alive, and survival status

- Calculate R^2_{trial} and R^2_{indiv} for each phase II outcome measure using relevant methodology

Treatment effect on response vs. OS

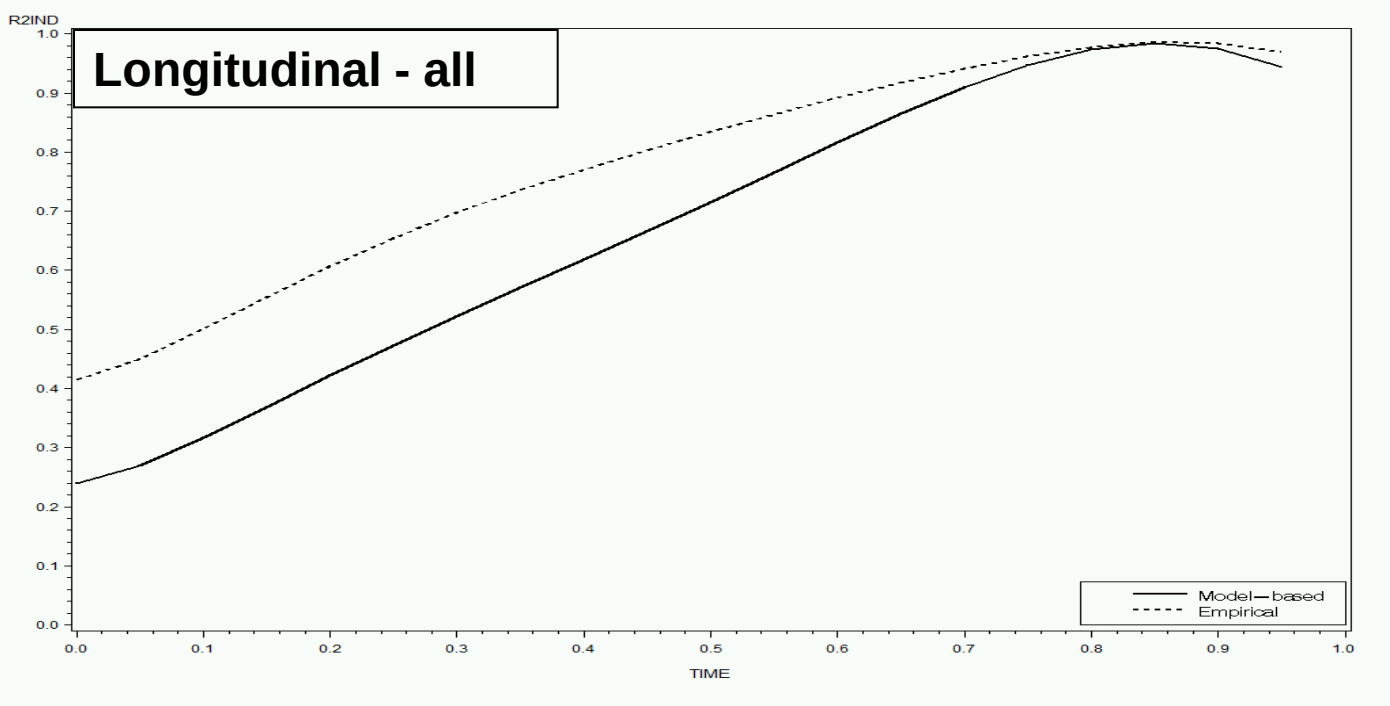


Comparison of R^2_{trial}



Comparison of R^2_{indiv}

	θ (95% CI)	τ (95% CI)
Response	0.22 (0.19, 0.27)	-
Non-progression	0.16 (0.14, 0.18)	-
PFS – all	-	0.54 (0.53,0.56)
PFS – 24w	-	0.49 (0.48,0.51)
PFS – 12w	-	0.46 (0.44,0.48)



Identifying the optimal outcome measure

- Easy option – pick the outcome measure with highest R^2_{trial}
  - Are the CIs too wide to be informative? – consider alternative grouping units, e.g. country
  - Is the lack of treatment effect on OS reflective of the impact of further lines of therapy? – consider alternative phase III outcomes, e.g. PFS

- Alternative ways to investigate the phase II outcome most appropriate
  - Consider prediction intervals and STE
  - Standardised assessment of R^2_{indiv}
  - Simulation of phase II and III trials

References

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Thank you

Email: **s.brown@leeds.ac.uk**

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