



CDDF MULTI-STAKEHOLDER WORKSHOP
MINIMAL RESIDUAL DISEASE

18-19 October 2017
London, UK

Clinical Development Strategy for validation of MRD as a surrogate endpoint

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Concept of surrogacy

- Need to understand the relationship between the 2 outcomes: MRD and PFS
- Surrogate = MRD outcome
- True = PFS outcome

(the following is based around work done by Sarah Brown at the Leeds CTRU)



Surrogacy methodology - options

- Consider the relationship between surrogate and true endpoints in terms of:
 - Treatment effects
 - Individual patient outcomes
- Have already used meta-analytic summary data to consider the *prognostic* relationship between surrogate (MRD) and true endpoint (PFS) for individual patients
- To account for the fact that the true and surrogate outcomes are actually paired data, i.e. from the same person, need to *jointly model* the outcome data using IPD



Surrogacy methodology – meta-analytic IPD

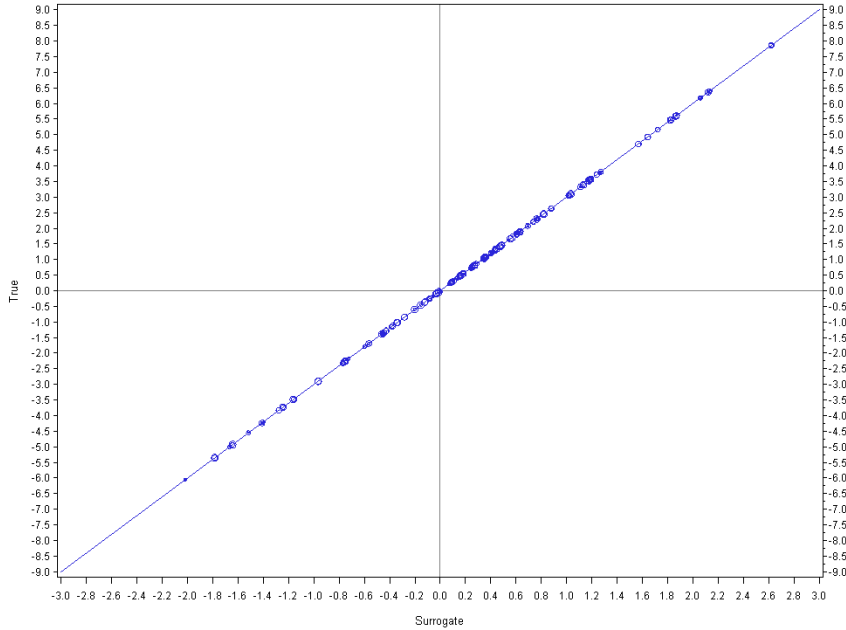
- Considers the strength of relationship between two outcome measures, and ***the ability of the treatment effect on the surrogate to predict the treatment effect on the true outcome measure***
- Has been used to assess the relationship between true and surrogate outcome measures, where the intention is to **replace** the true outcome with the surrogate
- Considers the ***joint distribution*** of the surrogate and true outcome measures, to estimate the treatment effect parameters, and the relationship between the two outcomes. ***This is not straightforward statistically!***



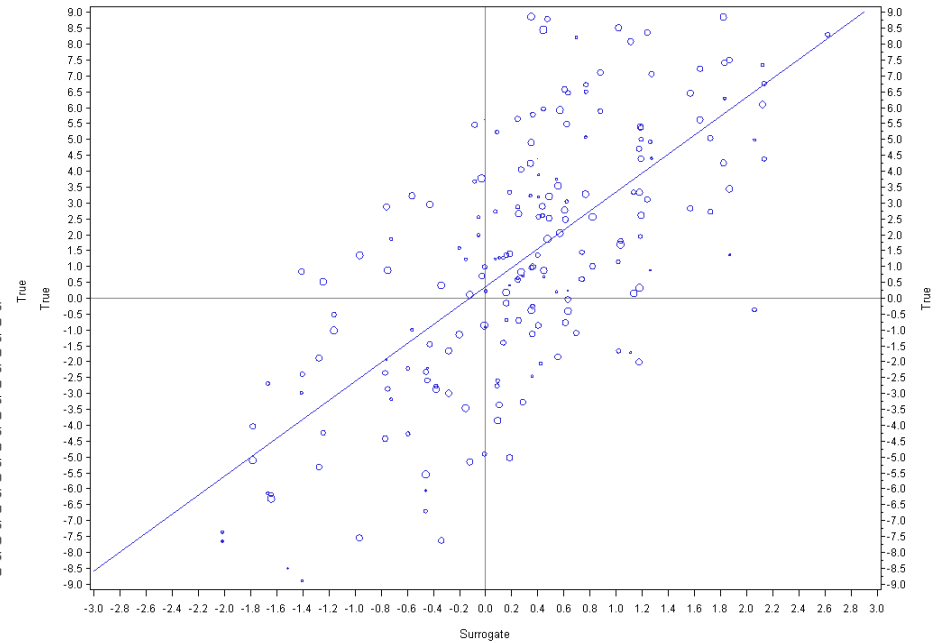


Quantifying surrogacy

- Surrogacy is assessed at two levels:
 1. Trial level – assesses the ability of the treatment effect on the surrogate outcome to predict the treatment effect on the true outcome – R^2_{trial}
 2. Individual level – assesses the association between the surrogate and true outcome after adjusting for treatment effects - R^2_{indiv}
- $R^2 = 1$ implies perfect surrogate, i.e. can replace true
- May not be looking to replace true outcome (PFS), but to get reliable intermediate outcomes to suggest further treatments or treatment alterations (eg switching of treatments, early stopping etc). So probably don't require R^2 to equal 1. What value do we want though?



$$R^2 = 1$$



$$R^2 = 0.5$$

R^2 = Coefficient of determination

At the individual level, each of these points is an individual patient

At the trial level, each of these points is a TRIAL



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Why do we need joint distributions?

- To account for the paired nature of the data and to estimate the treatment effects incorporating this
- To avoid ecologic bias – e.g. observe a treatment effect on both the surrogate and true endpoint, but the patients who have treatment benefit on the surrogate are NOT those who have treatment benefit on the true endpoint





How do we calculate R^2 ?

General method

- Use a two-stage approach to
 - 1) jointly model the two outcome measures and obtain parameter estimates of treatment effects
 - 2) Assess the relationship between the outcome measures based on the estimates obtained in stage 1
- Calculate R^2_{trial} based on treatment effects in each trial
- Stage 1 differs dependent upon the distributions of the true and surrogate endpoints (i.e. the approach to jointly modelling the data differs), so the summary for individual level surrogacy differs



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Example of using surrogacy methodology applied to phase II colorectal cancer trials

- Want to look at the relationship between phase II and phase III outcome measures using surrogacy methodology
- Specifically looking at advanced colorectal cancer (aCRC) – initial setting to provide example of using this methodology for this purpose
- For this example we want to consider the relationship between different phase II outcome measures on the same datasets





Data

- Individual patient data from 7 clinical trials of aCRC
- 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





Outcome measures

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

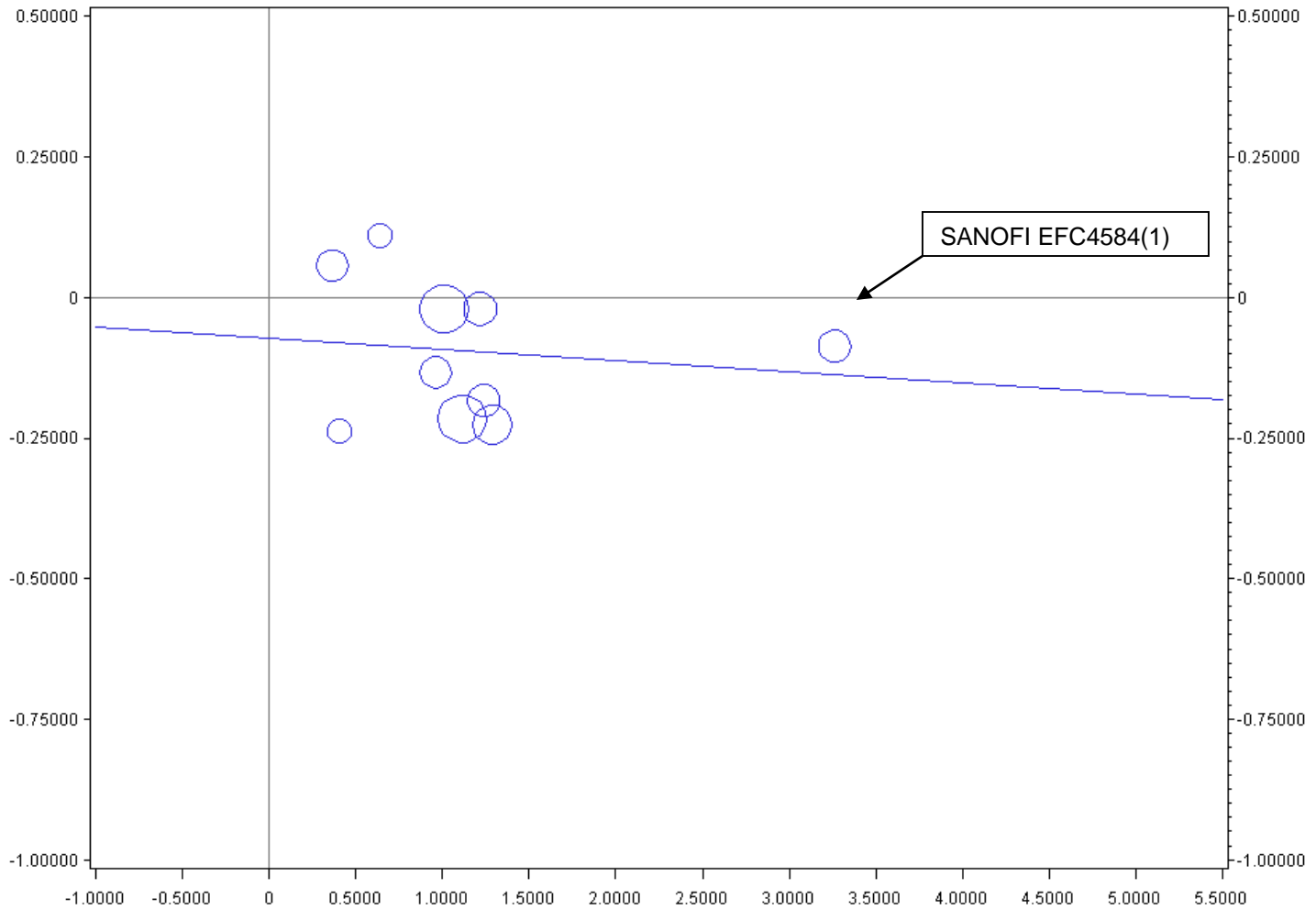


Methodology

- Use Copula functions to model the joint distributions.
- Different for binary/categorical measures/surrogates and longitudinal continuous measures and time-to-event measures (eg PFS)
- Obtain treatment effect parameters on the measure (eg response) and survival for each of the trials, from the joint model, and obtain the coefficient of determination R^2 , at the trial level



T
Treatment effect on survival=log(HR)



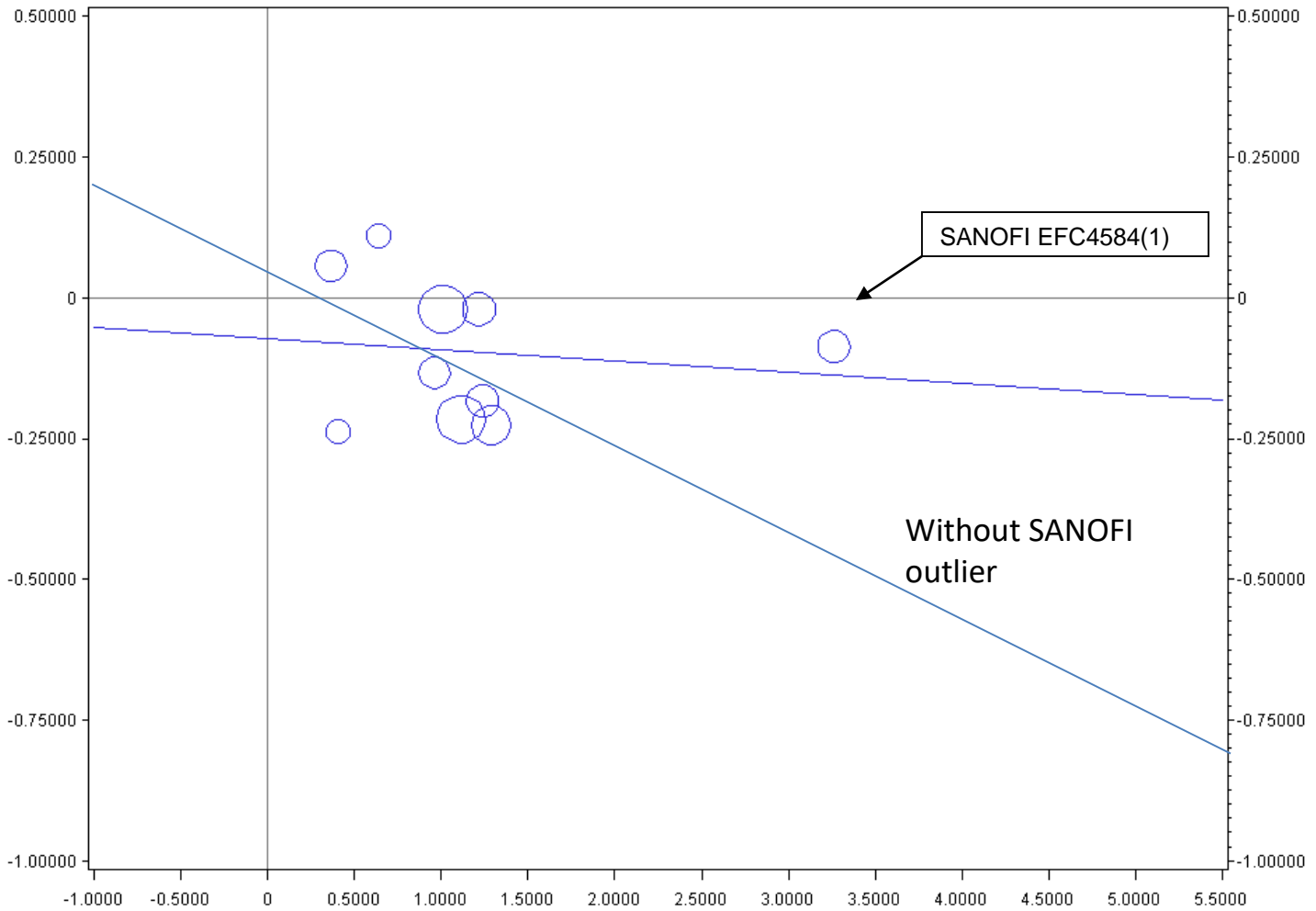
Regression Equation:
Estimate = -0.072688 - 0.019927*est

Treatment effect on tumour response=log(OR)





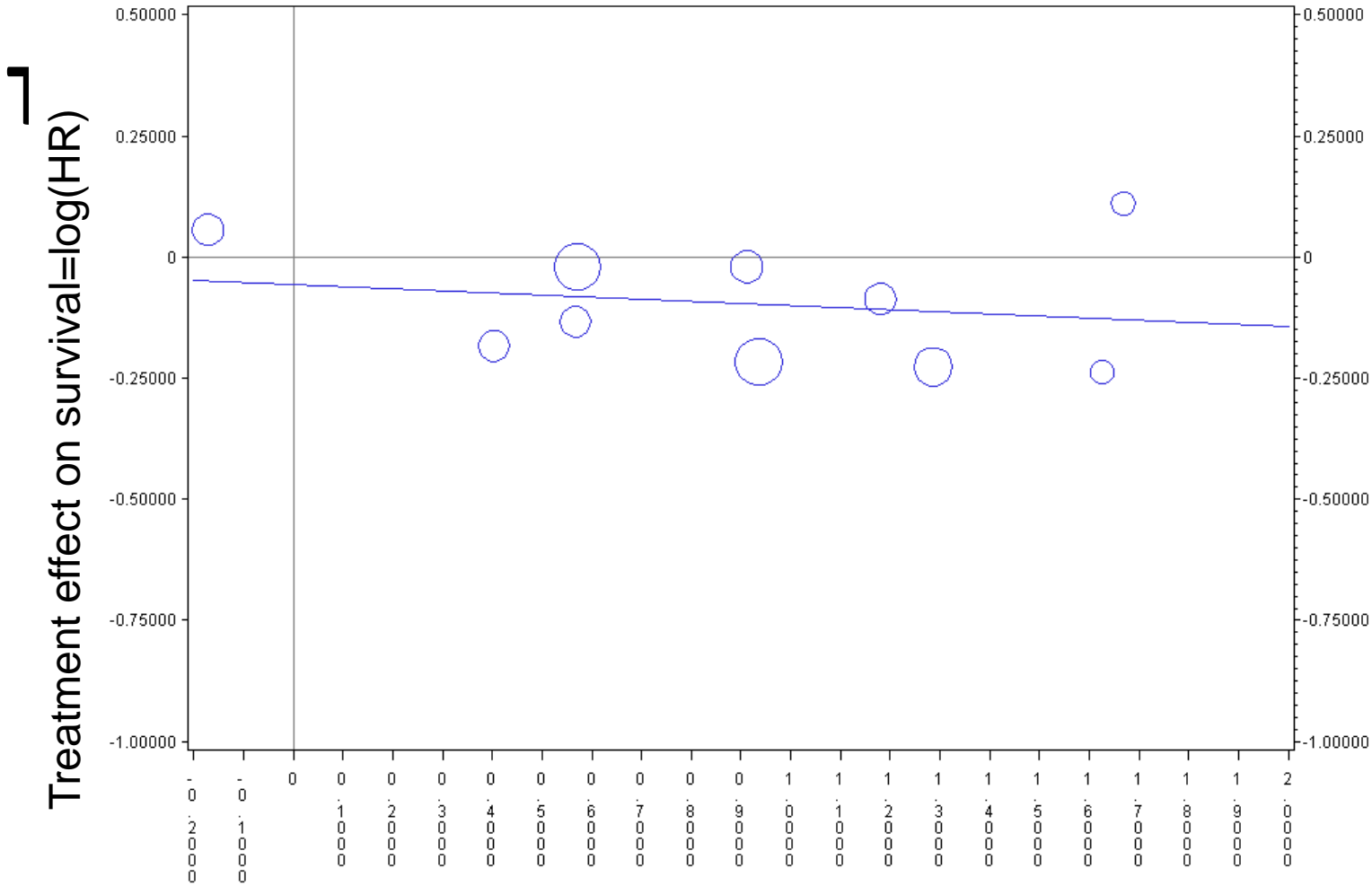
T
Treatment effect on survival=log(HR)



Regression Equation:
Estimate = -0.072688 - 0.019927*est

Treatment effect on tumour response=log(OR)





'S.

Treatment effect on non-progression=log(OR)

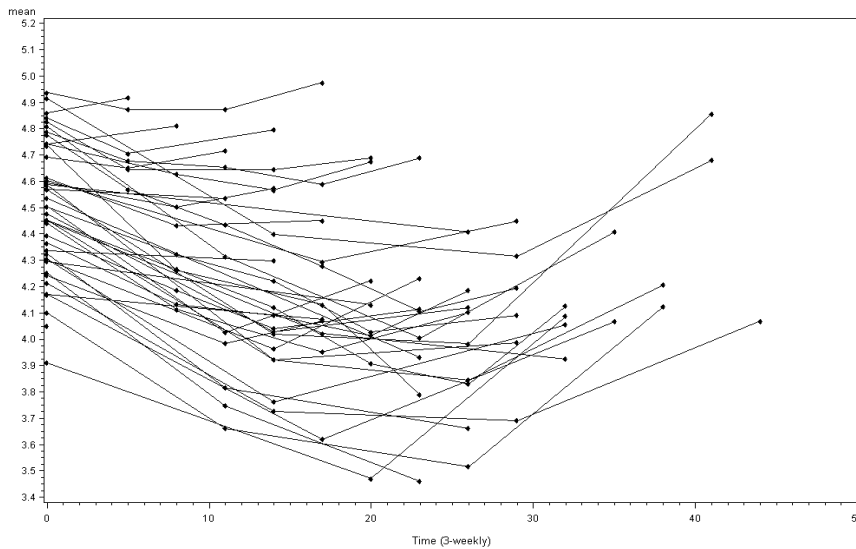
Regression Equation:
Estimate = -0.056759 - 0.043255*est2



Continuous tumour measures: Longitudinal profiles (log(SLD)) to progression

02JUL11 - Longitudinal continuous tumour measurements - data summaries

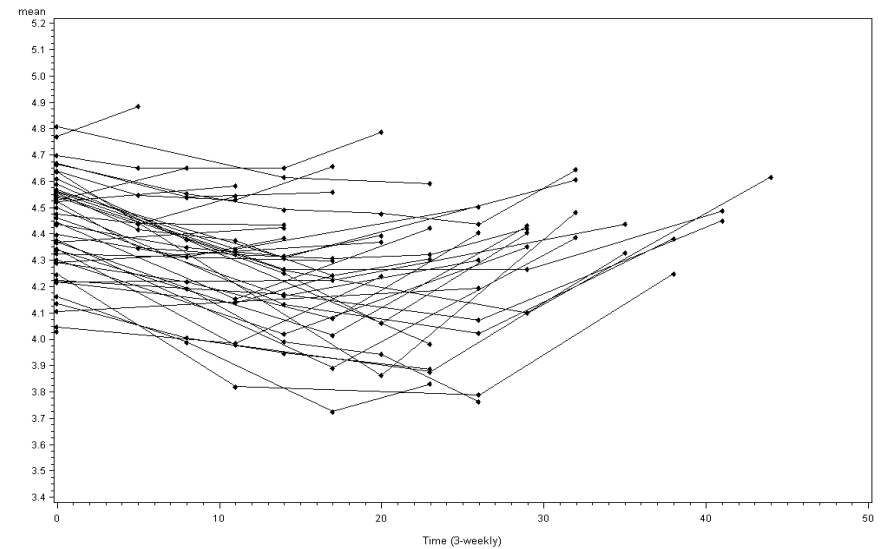
Log tumour measurements according to last tumour measurement to progression
for 3-weekly patterns of assessment with at least 15 patients
treat=1



Experimental

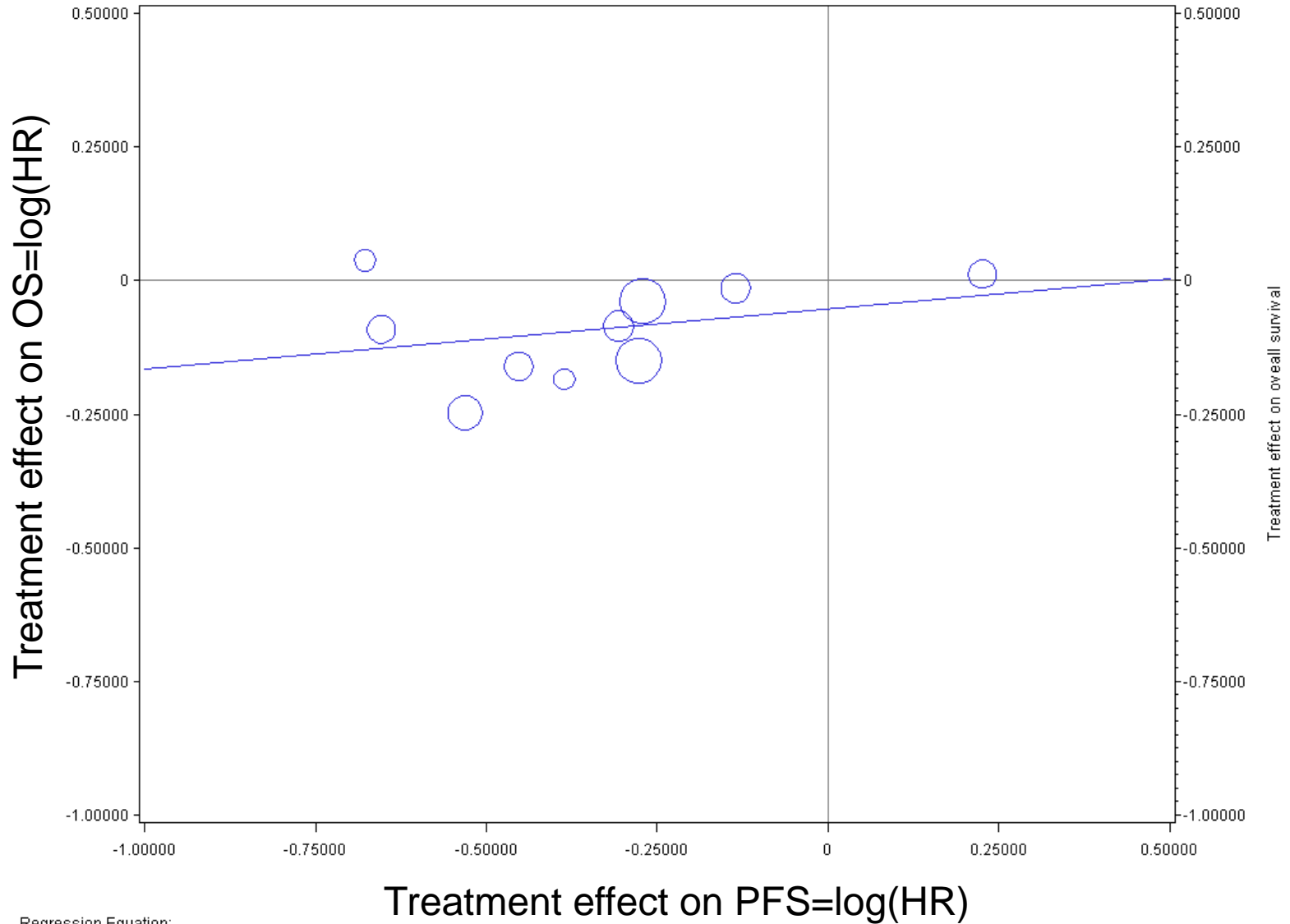
02JUL11 - Longitudinal continuous tumour measurements - data summaries

Log tumour measurements according to last tumour measurement to progression
for 3-weekly patterns of assessment with at least 15 patients
treat=0



Control

Model fit: $\log(\text{sld}) = \text{time}^{1.5} + \text{time}^2$



Regression Equation:
Estimate = -0.05247 + 0.114057*estimatep





Summary of relationship with OS

	$R^2_{\text{trial}(N)}$	θ	τ
Response (excl.)	0.265 (<0, 0.682)	0.22 (0.19, 0.24)	-
Non-progression	0.163(<0, 0.571)	0.16 (0.14, 0.18)	-
Longitudinal – all	0.721 (<0,0.891)	-	-
PFS – all	0.477 (<0, 0.822)	-	0.54 (0.53,0.56)



Potential issues for the example in aCRC

- Are the R^2 values comparable?
- Wide CIs
- Issues in calculating adjusted R^2 (to adjust for estimation bias)
- Is this data just not sufficient for this methodology?
- Use of survival as gold standard outcome for phase III – post-progression survival an issue due to many further line treatments



References

- Brown, SR. Optimising the design of phase II trials in cancer. June 2012 PhD Thesis
- Brown et al. Designing phase II trials in cancer: a systematic review and guidance. *BJC* 2011; 105: 194-199
- Burzykowski et al. The validation of surrogate end points by using data from randomized clinical trials: a case-study in advanced colorectal cancer. *JRSS(Series A)* 2004; 167: 103-124
- Buyse et al. Progression-Free Survival Is a Surrogate for Survival in Advanced Colorectal Cancer. *JCO* 2007; 25: 5218-5224
- Renard et al. Validation of a longitudinally measured surrogate marker for a time-to-event endpoint *J. Appl. Stat* 2003; 30: 235-247
- Burzykowski et al. Validation of surrogate endpoints in multiple randomised clinical trials with failure-time endpoints. *Appl. Stat* 2001; 50: 405-422





MRD surrogacy analyses: requirements – trials/data sets

To make this work we need a sizeable number of trial data sets - so that we have enough data points & variability on the correlation graphs to get reasonable estimates/CIs (to convince regulators!)

We can potentially use more than one 'unit' from an individual trial, e.g. for Myeloma IX & Myeloma XI TE and TNE can be considered separate data sets for the purposes of the surrogacy analyses.

Ideally need of the order of 15 trial 'units' (or more) – also need spread of results i.e. variability in magnitude of treatment effects



Available MRD data sets

- **Myeloma IX:**

397 TE patients, 245 TNE patients:- as in the 3 publications:

Multiparameter Flow Cytometry in Multiple Myeloma: Impact on Outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol*. 2013 Jul 10;31(20):2540-7.

Minimal residual disease in myeloma by flow cytometry: Independent prediction of survival benefit per log reduction. *Blood* 2015 125(12), 1932-1935.

Minimal Residual Disease Following Autologous Stem Cell Transplant In Myeloma: Impact On Outcome Is Independent Of Induction Regimen. *Haematologica*, 101(2), e69-e71.



Available MRD data sets

Myeloma XI:

Data available at following timepoints:

post-induction, post-VCD, post-transplant and 6m post-maintenance

>389 TE patients with MRD data currently available

297 TNE patients with MRD data currently available

389 with informative MRD 6 months post-maintenance randomisation (+ end induction & prior to maintenance)



MRD as a surrogate for PFS – what do we need operationally?

- Centralised database
- Multiple trial datasets in same population
- Individual patient data including:
 - Patient characteristics
 - Treatment received
 - Standardised endpoint data – MRD, PFS, OS
- Pre-agreed statistical analysis plan with full definition of endpoints
- Data sharing agreements
- Staffing – statistics; data management; trial management; IT



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Additional methodology slides if
required





Methodology (1)

Binary/categorical surrogate

- Use a Copula function as the joint distribution; this provides an association parameter which can be interpreted as a global odds ratio, θ , of survival for responders vs. non-responders (θ is a representation of R^2 at the individual level)
- Obtain treatment effect parameters on response and survival for each of the trials, from the joint model, and obtain the coefficient of determination R^2 , at the trial level



Methodology (2)

Longitudinal continuous measures

- Identify a model of best fit to describe the trajectory of the longitudinal data
- Model the longitudinal data via a linear mixed effects model
- Describe the association between the longitudinal data and OS via a latent bivariate process, i.e. assume that the relationship can be described by the random effects
- Summarise R^2_{indiv} as a time dependent estimate of the squared correlation between the latent processes
- Determine R^2_{trial} by regression of the treatment effects on the longitudinal measure on the treatment effect on OS



Methodology (3)

Progression-free survival

- As for binary surrogates, use a Copula function as the joint survival distribution function for PFS and OS
- Here, however, the Copula function is transformed to calculate Kendall's τ , rather than using the Copula parameter θ to describe the association at the individual level
- Obtain treatment effect parameters on PFS and OS for each of the trials, from this joint model, and obtain the coefficient of determination R^2 , at the trial level



Methodology note

- In estimating R^2_{trial} by the coefficient of determination, an element of estimation bias is introduced. The error associated with estimating the treatment effects in the first step of the 2-stage process is ignored in the methods discussed so far to calculate R^2_{trial} . Adjusted estimates accounting for this estimation error may also be calculated