Supplementary material to

Multi-state models for colon cancer recurrence and death with a cured fraction

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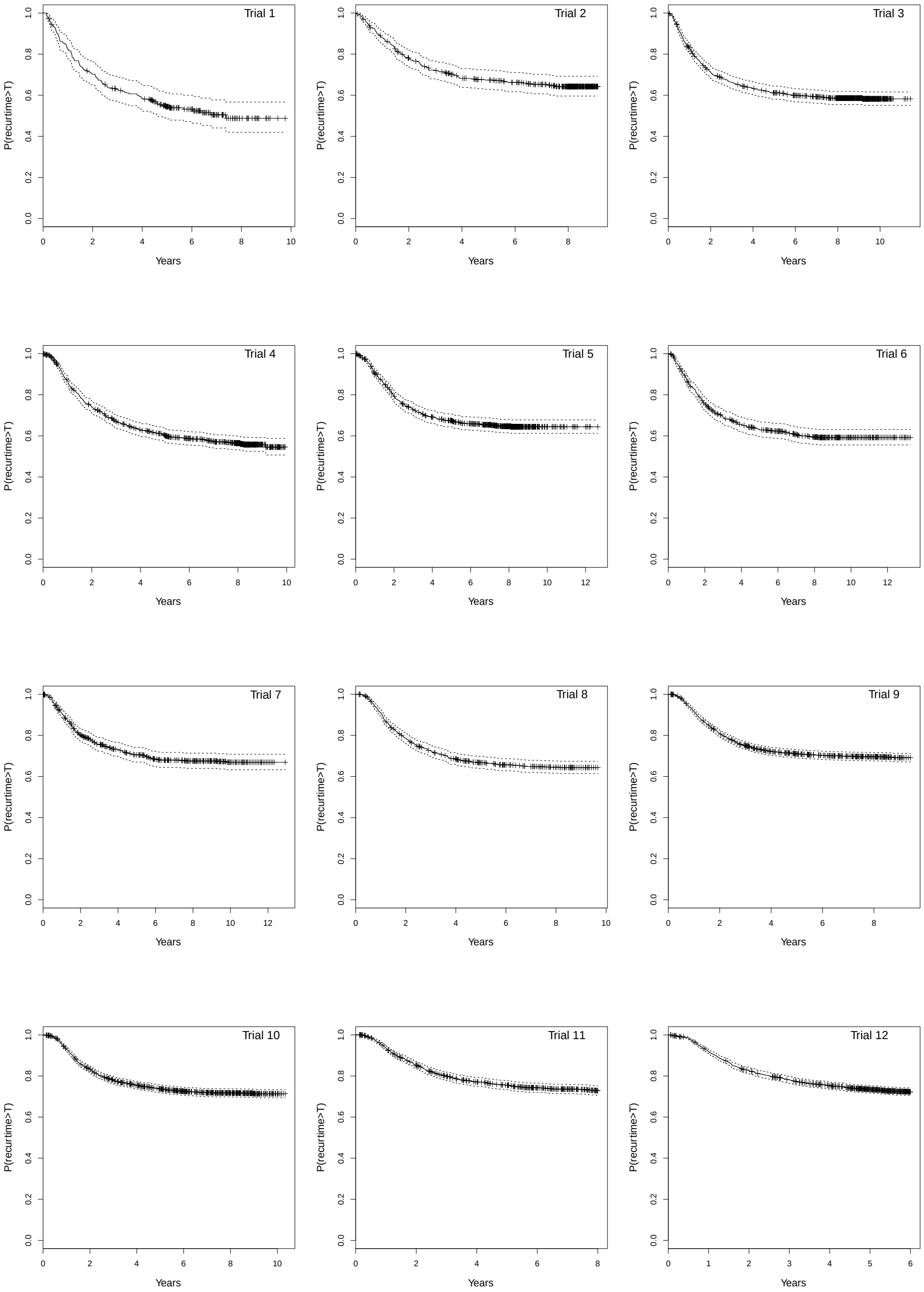
Appendix A: Kaplan-Meier plots of time to recurrence

Kaplan-Meier plots of time to recurrence for the 12 trials. Patients who died without recurrence are censored for recurrence at that time.



Appendix B: Details of Estimation Procedure

Define the following indicator functions:

$RD_i = I(\delta_{ir} = 1, \delta_{id} = 1, Y_{ir} < Y_{id})$
$RDs_i = I(\delta_{ir} = 1, \delta_{id} = 1, Y_{ir} = Y_{id})$
$RA_i = I(\delta_{ir} = 1, \delta_{id} = 0, Y_{ir} < Y_{id})$
$RAs_i = I(\delta_{ir} = 1, \delta_{id} = 0, Y_{ir} = Y_{id})$
$RAs_i = I(\delta_{ir} = 1, \delta_{id} = 0, Y_{ir} = Y_{id})$
$NRD_i = I(\delta_{ir} = 0, \delta_{id} = 1, Y_{ir} < Y_{id})$
$NRA_i = I(\delta_{ir} = 0, \delta_{id} = 0, Y_{ir} < Y_{id})$
$NRDs_i = I(\delta_{ir} = 0, \delta_{id} = 1, Y_{ir} = Y_{id})$
$NRAs_i = I(\delta_{ir} = 0, \delta_{id} = 0, Y_{ir} = Y_{id})$
$Z_i = I(c_i = 1)$

The observed data likelihood is given by:

$\prod_{i=1}^{n} \{ \ [(1-p_i)S_2(Y_{ir})\lambda_{23}(Y_{ir})S_3(Y_{id})\lambda_{34}(Y_{id}-Y_{ir})]^{RD_i(1-Z_i)}$
$[(1-p_i)\int_0^{Y_{ir}} \lambda_{23}(u)S_2(u)\lambda_{34}(Y_{id}-u)^{\delta_{id}}S_3(Y_{id} \mid u)du]^{RDs_i(1-Z_i)}$
$[(1-p_i)S_2(Y_{ir})\lambda_{23}(Y_{ir})S_3(Y_{id})]^{RA_i(1-Z_i)}$
$[(1-p_i)S_2(Y_{ir})\lambda_{23}(Y_{ir})]^{RAs_i(1-Z_i)}$
$[p_i\lambda_{14}(Y_{id})S_1(Y_{id})]^{NRD_iZ_i}$
$[(1-p_i)\lambda_{24}(Y_{id})S_2(Y_{id})+(1-p_i)\int_{Y_{ir}}^{Y_{id}} \lambda_{23}(u)S_2(u)\lambda_{34}(Y_{id}-u)S_3(Y_{id} \mid u)du]^{NRD_i(1-Z_i)}$
$[p_iS_1(Y_{id})\lambda_{14}(Y_{id})]^{NRDs_iZ_i}$
$[(1-p_i)S_2(Y_{id})\lambda_{24}(Y_{id})]^{NRDs_i(1-Z_i)}$
$[p_iS_1(Y_{id})]^{NRA_iZ_i}$
$[(1-p_i)S_2(Y_{id}) + (1-p_i)\int_{Y_{ir}}^{Y_{id}} \lambda_{23}(u)S_2(u)S_3(Y_{id} \mid u)du]^{NRA_i(1-Z_i)}$
$[p_iS_1(Y_{id})]^{NRAs_iZ_i}$
$[(1-p_i)S_2(Y_{id})]^{NRAs_i(1-Z_i)}\}$

Where:

$p_i = \frac{exp(\gamma_0+\gamma_{trt}T_i+\gamma_{st}S_i+\gamma_{age}A_i)}{1+exp(\gamma_0+\gamma_{trt}T_i+\gamma_{st}S_i+\gamma_{age}A_i)}$
$S_1(t) = exp\left(-\left(\frac{t}{\lambda_{14}}\right)^{\rho_{14}} exp(\beta_{trt_{14}}T_i + \beta_{st_{14}}S_i + \beta_{age_{14}}A_i)\right)$
$S_2(t) = exp\left(-\left(\frac{t}{\lambda_{23}}\right)^{\rho_{23}} exp(\beta_{trt_{23}}T_i + \beta_{st_{23}}S_i + \beta_{age_{23}}A_i) - \left(\frac{t}{\lambda_{24}}\right)^{\rho_{24}} exp(\beta_{trt_{24}}T_i + \beta_{st_{24}}S_i + \beta_{age_{24}}\right.$
$S_3(t) = exp\left(-\left(\frac{t-Y_{ir}}{\lambda_{34}}\right)^{\rho_{34}} exp(\beta_{trt_{34}}T_i + \beta_{st_{34}}S_i + \beta_{age_{34}}A_i + \beta_{Tr_{34}}Y_{ir})\right)$
$\lambda_{23}(t) = \left(\frac{\rho_{23}}{\lambda_{23}}\right)\left(\frac{t}{\lambda_{23}}\right)^{\rho_{23}-1} exp(\beta_{trt_{23}}T_i + \beta_{st_{23}}S_i + \beta_{age_{23}}A_i)$
$\lambda_{24}(t) = \left(\frac{\rho_{24}}{\lambda_{24}}\right)\left(\frac{t}{\lambda_{24}}\right)^{\rho_{24}-1} exp(\beta_{trt_{24}}T_i + \beta_{st_{24}}S_i + \beta_{age_{24}}A_i)$
$\lambda_{34}(t-Y_{ir}) = \left(\frac{\rho_{34}}{\lambda_{34}}\right)\left(\frac{(t-Y_{ir})}{\lambda}\right)^{\rho_{34}-1} exp(\beta_{trt_{34}}T_i + \beta_{st_{34}}S_i + \beta_{age_{34}}A_i + \beta_{Tr_{34}}Y_{ir})$

The integrals:

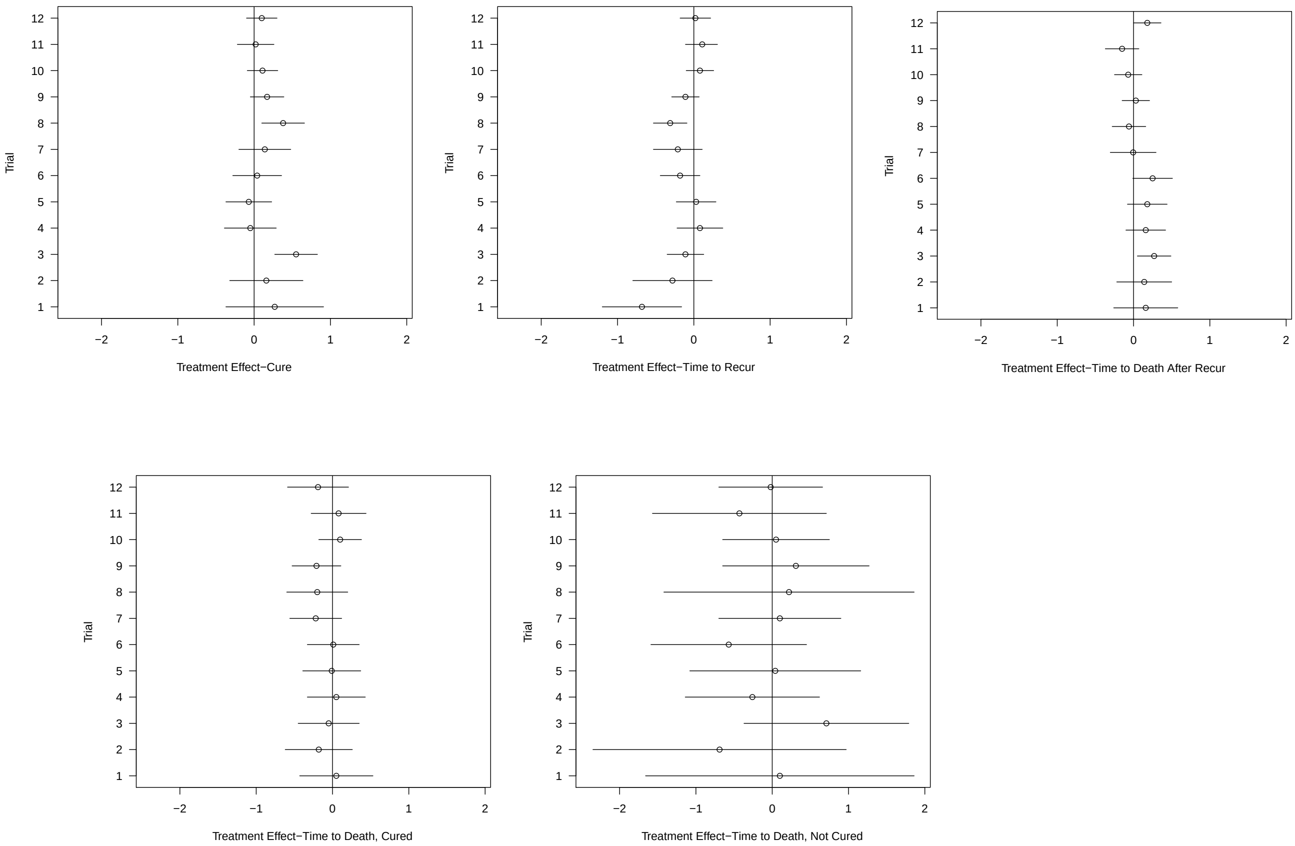
$\int_0^{Y_{ir}} \lambda_{23}(u)S_2(u)\lambda_{34}(Y_{id}-u)^{\delta_{id}}S_3(Y_{id} \mid u)du$

$\int_{Y_{ir}}^{Y_{id}} \lambda_{23}(u)S_2(u)\lambda_{34}(Y_{id} - u)^{\delta_{id}} S_3(Y_{id} \mid u)du$
were computed by adaptive quadrature using the 'integrate' function in R.

The Metropolis-Hastings algorithm is used to draw parameters. The chain is run for 50,000 iterations, after a 10,000 iteration burn-in period with 5,000 draws from the posterior distribution saved for each parameter by taking every 100th draw from the post burn-in iterations. All of the proposal distributions are normal and centered at the most recent parameter draw. For the shape parameters, the proposal distribution is truncated at 0. For each study, the variance of the proposal distribution for each parameter is adjusted so that each of the resulting acceptance rates are close to 40%.

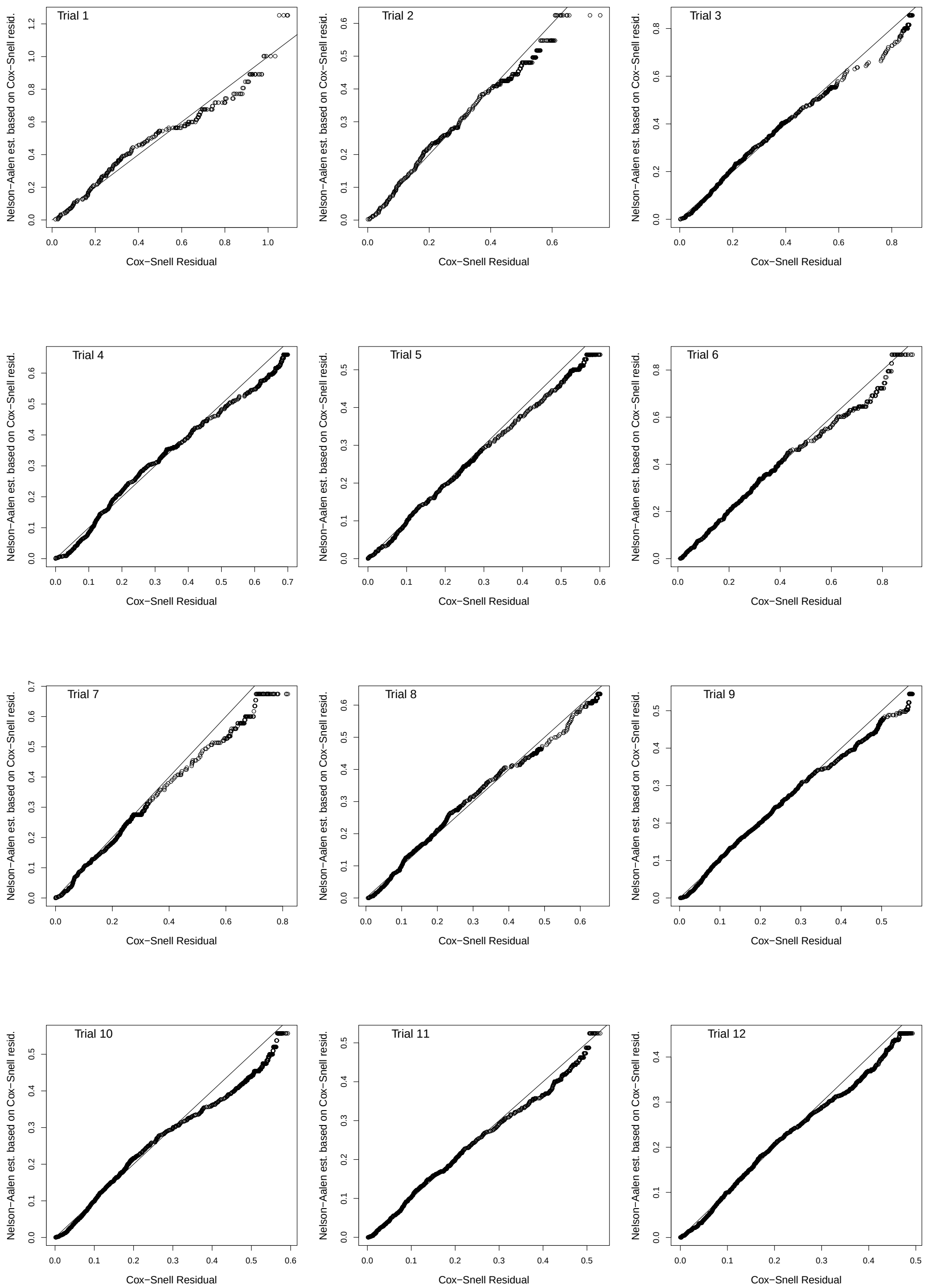
Appendix C: Treatment Effects

Figure A1: Treatment effect estimates for each of the five model compenets for 12 trials. Each line represents the 95% credible interval for the coefficient.

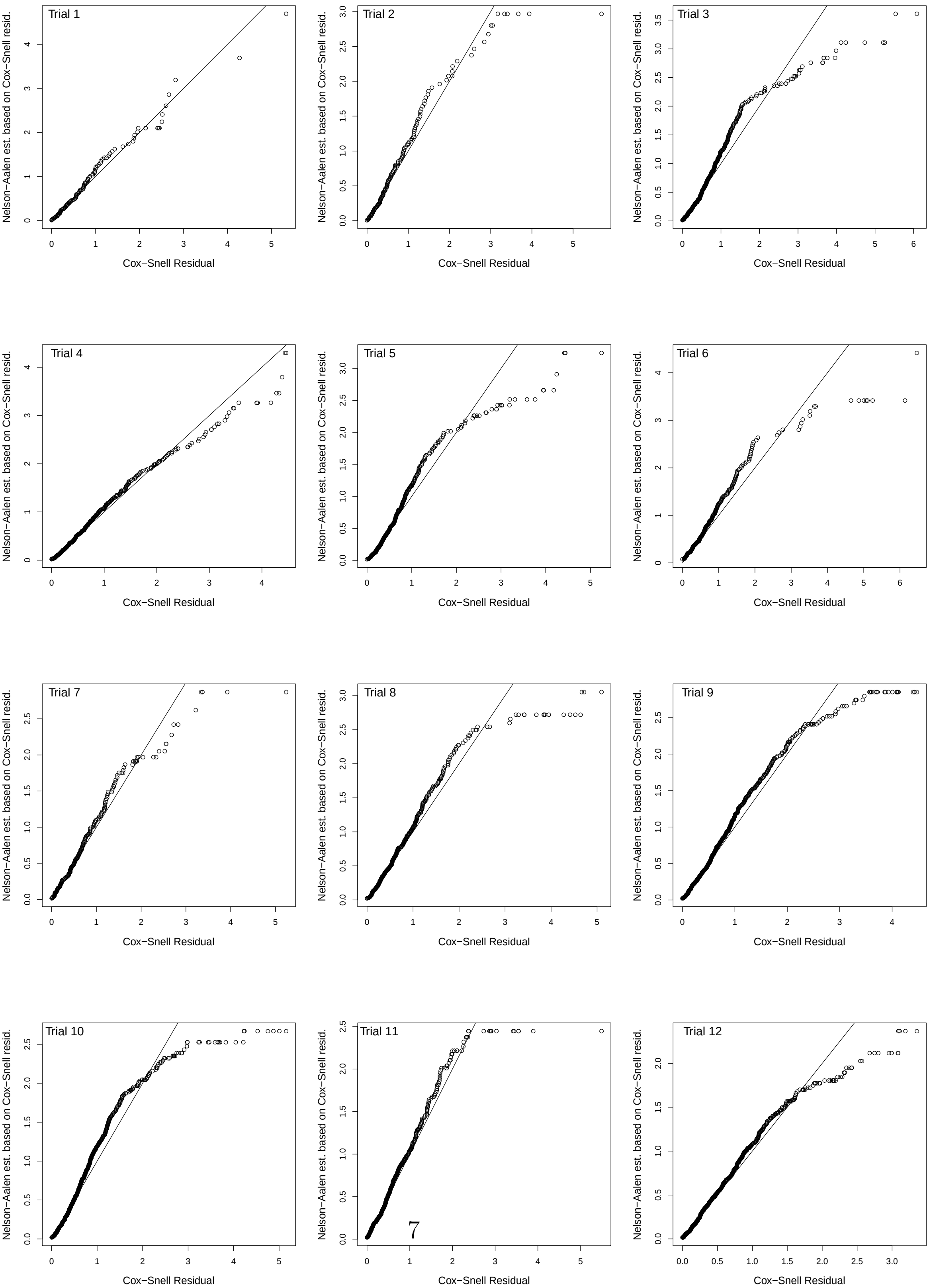


Appendix D: Cox-Snell residual plots

Cox-Snell residual plots for time to recur. Results from 12 trials.

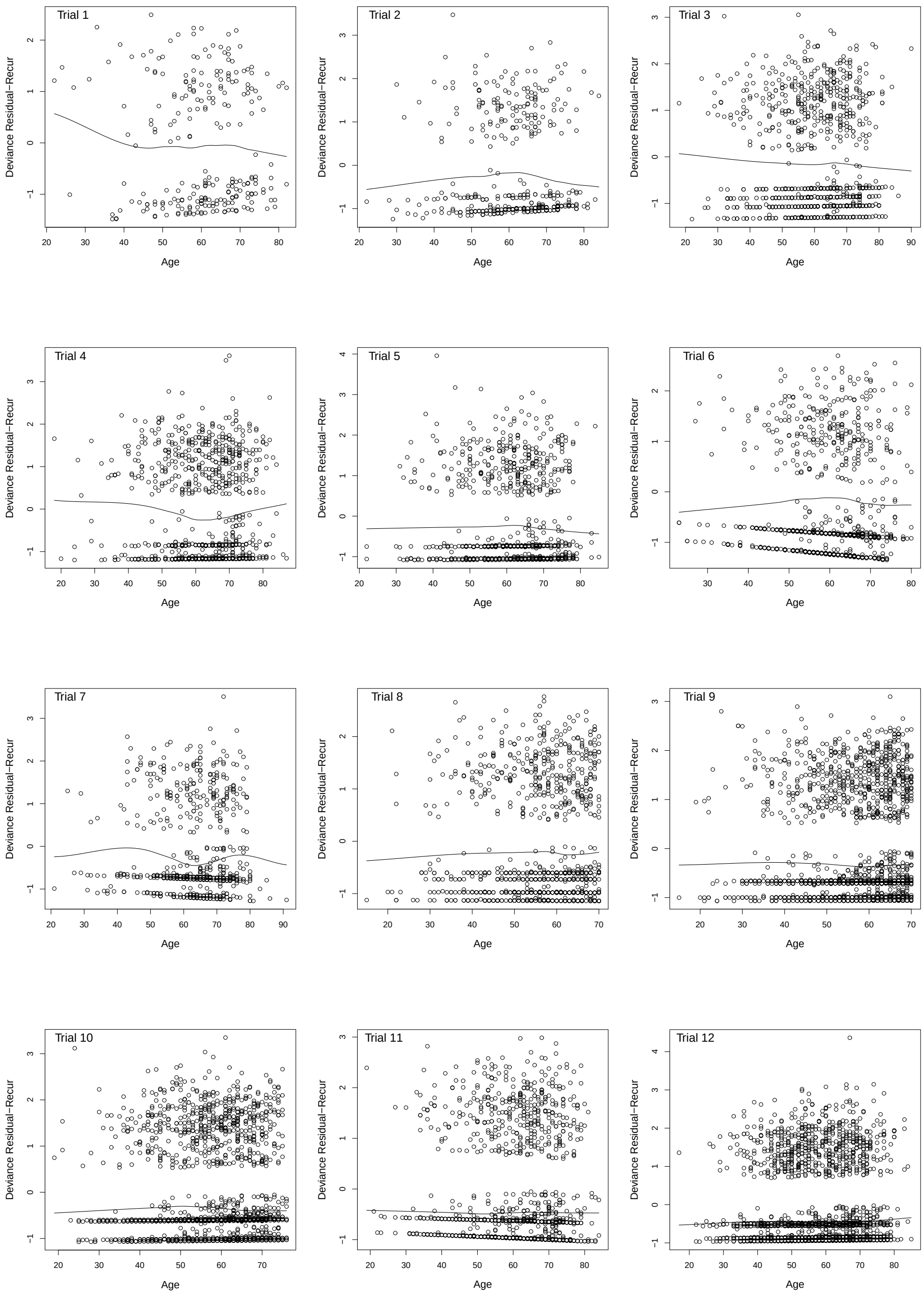


Cox-Snell residual plots for time to death after recur. Results for 12 trials.

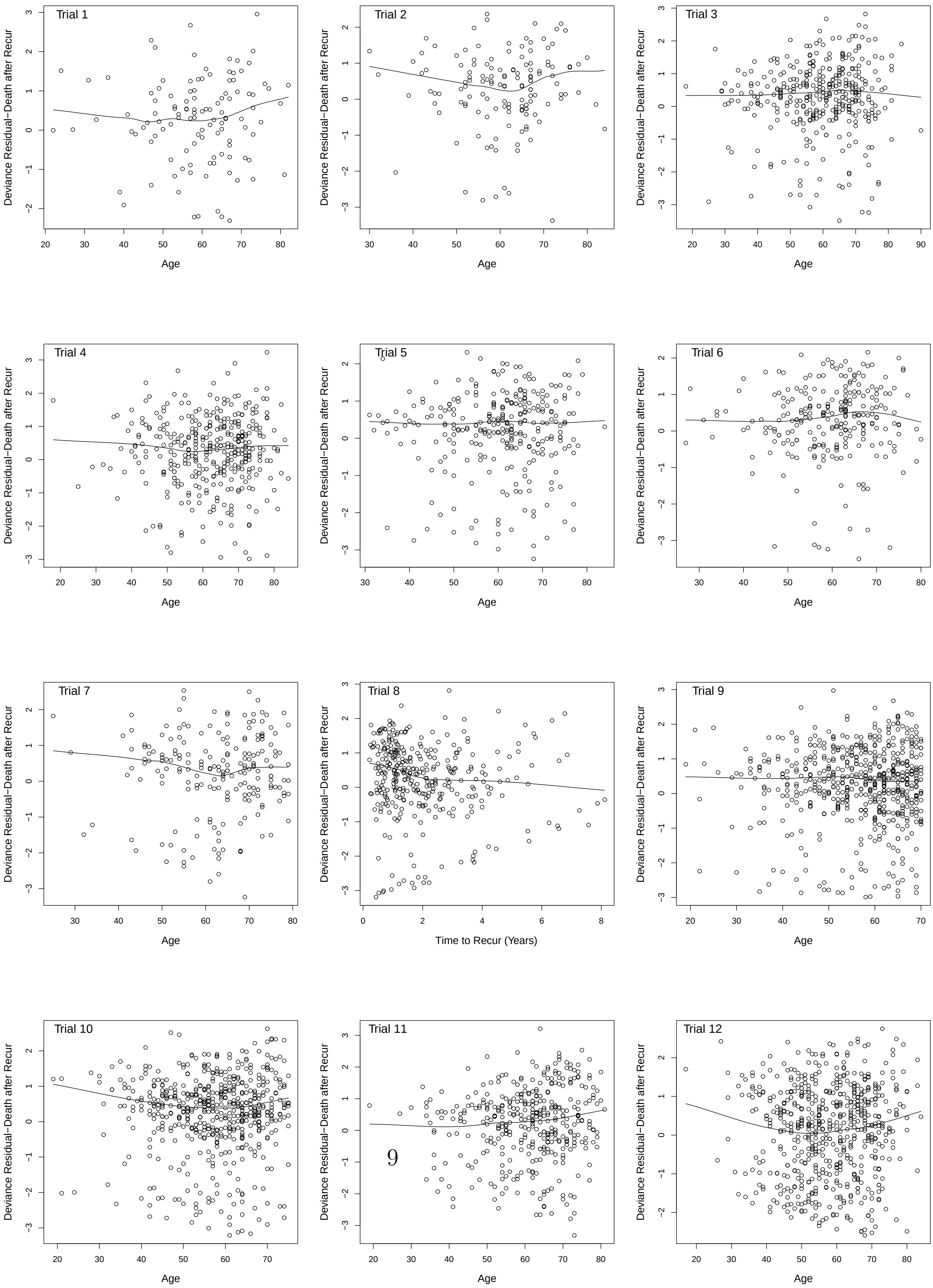


Appendix E: Deviance residual plots

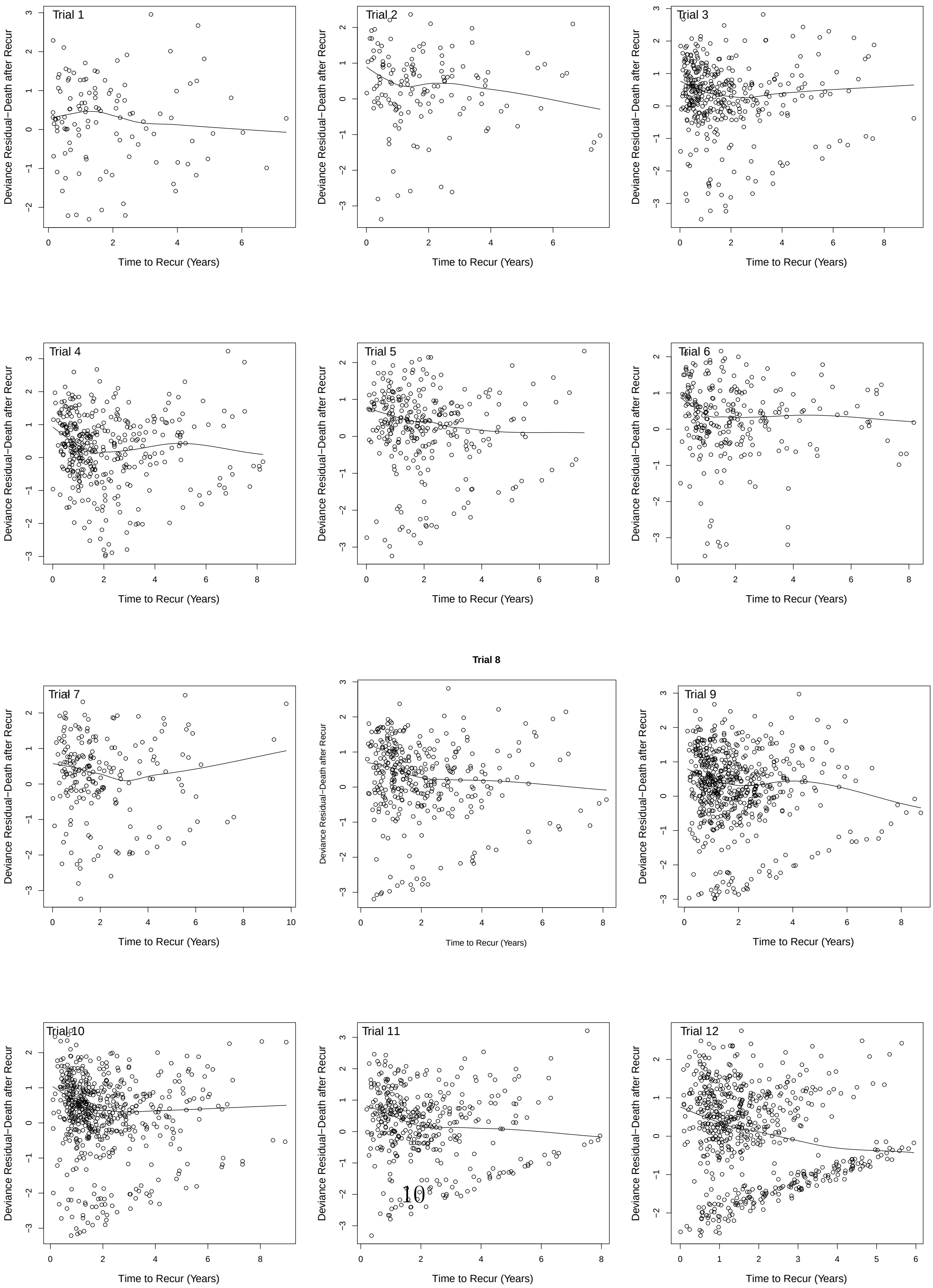
Deviance residual plots for time to recurrence plotted against age.



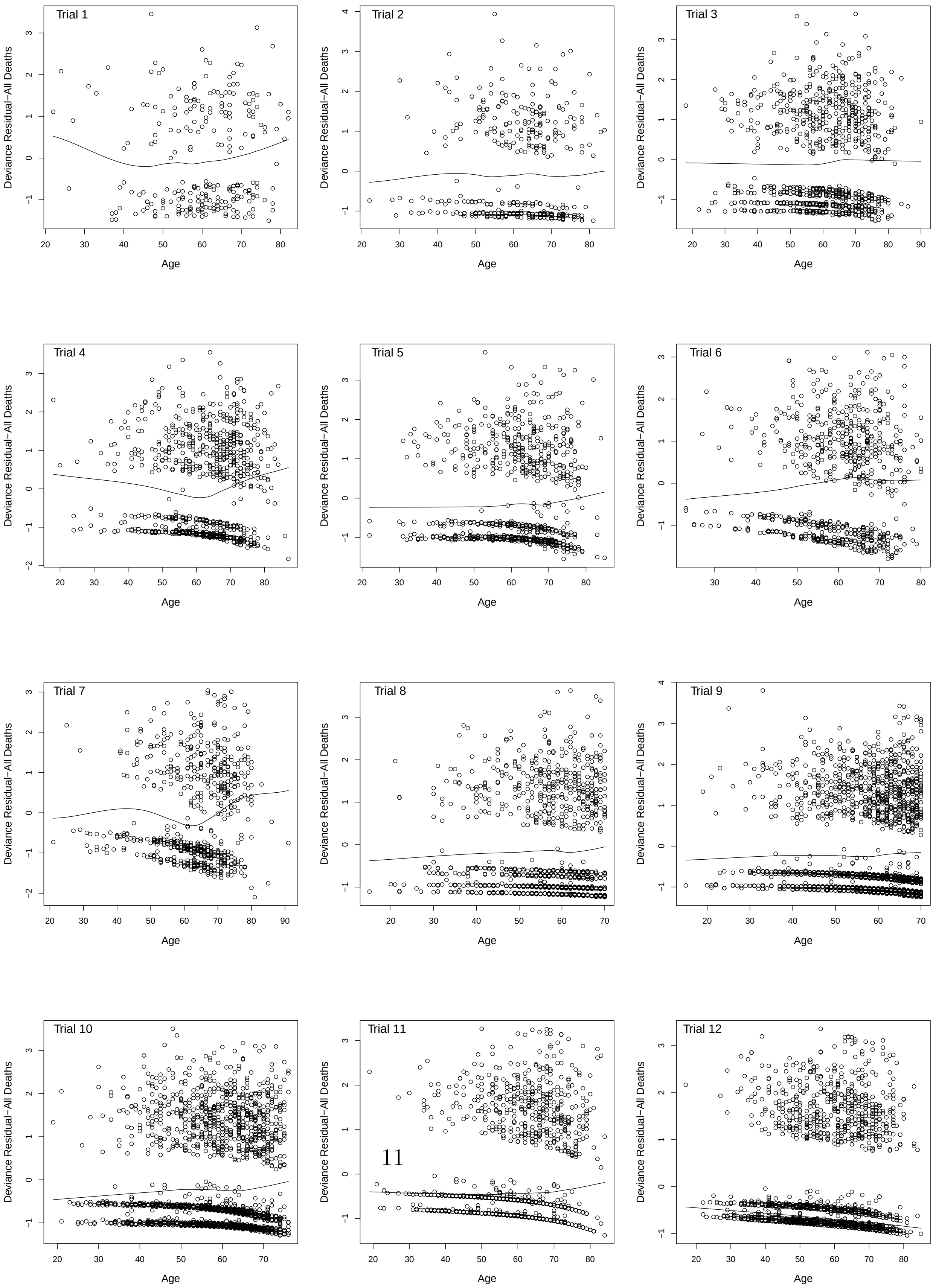
Deviance residual plots for time to death after recurrence plotted against age.



Deviance residual plots for time to death after recurrence plotted against time to recurrence.



Deviance residual plots for time to death plotted against age.



Appendix F: Cox-Snell residual plots for the model with no cured fraction

Cox-Snell residual plots for time to death for model without a cured fraction. Results from 12 trials.