

Use of early longitudinal viral load as a surrogate to the virologic endpoint in Hepatitis C: a semi-parametric mixed effect approach using SAS®

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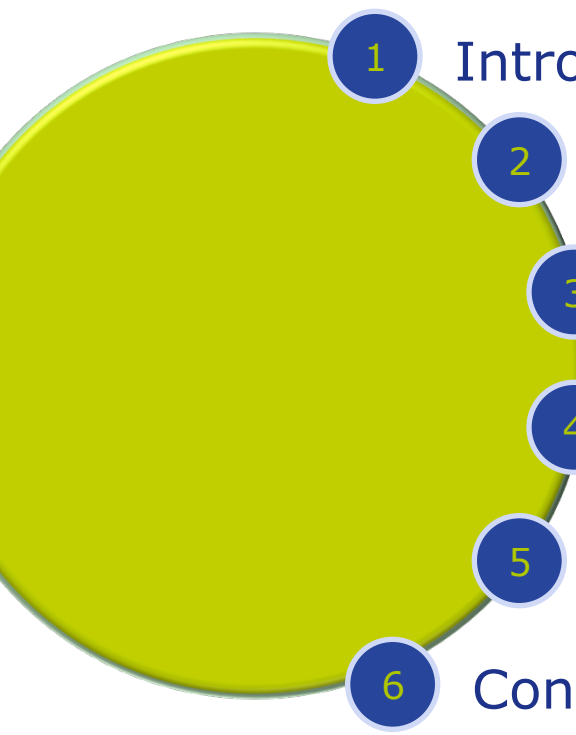
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Introduction

- The use of surrogate endpoints in clinical trials is increasing, necessitating the development of sound statistical methods in the validation process (Burzykowski et al. 2005).
- Although the idea of surrogacy was developed in the context of single trial (Prentice 1989, Freedman et al.1992, Buyse and Molenberghs 1998), the meta-analytic approach is now a well accepted one.
- The meta-analytic approach allows both individual and trial level surrogacy.
- For our purposes, we shall keep to individual level surrogacy.

Introduction (contd.)

- Important implications of statistical validation of surrogate:
 - A prediction but also discriminative model is needed.
 - Validity of a surrogate = quality of prediction.
 - Model extrapolation to a new treatment (mechanism)?
- Typically in HCV trials, patients receive 24/48 weeks of treatment and are then followed up for 24 weeks before assessing the primary efficacy endpoint.
- Throughout the duration of the study, HCV viral RNA is continually evaluated resulting in longitudinal measurements.

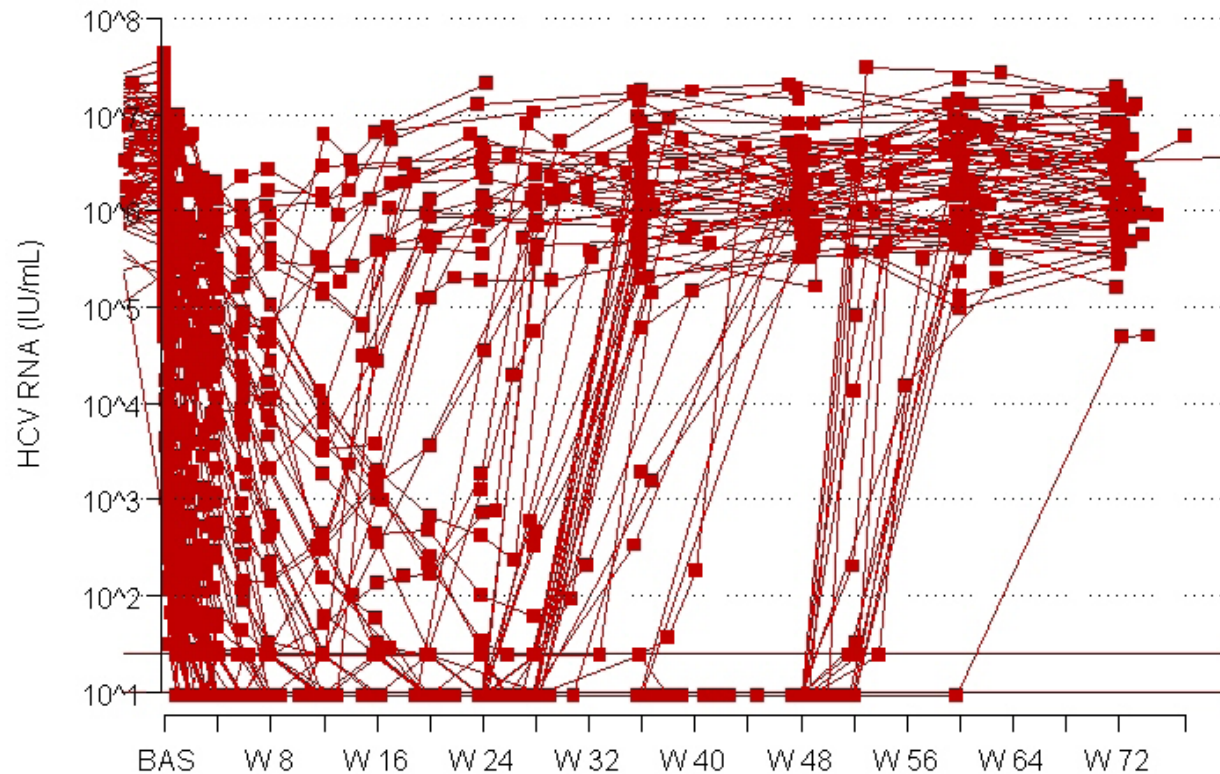
Research Question:

- Can the first few Measurements in the Longitudinal Sequence be used as a Surrogate to the Virologic Endpoint in Hepatitis C Virus (HCV) Infection Trials?

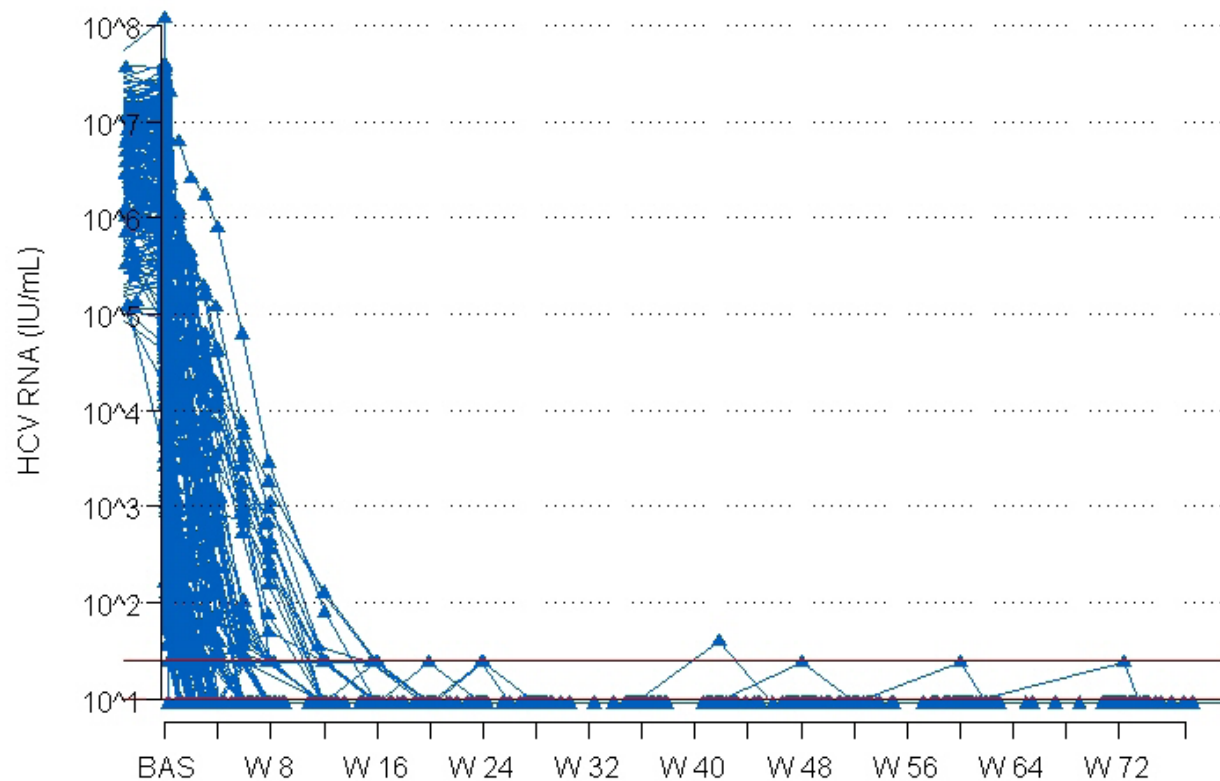
The HCV protease inhibitor data description

- Phase IIb, randomized, double-blind, placebo-controlled trial to compare the efficacy, tolerability and safety of different regimens with Direct Antiviral (DA) plus PegIFN-2a and RBV versus PegIFN-2a plus RBV alone in adult treatment-naïve subjects with genotype 1 HCV infection.
- Measurements taken at week: 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 36, 48, 60 and 72.
- Analysis limited to the data obtained from the first 12 weeks.
- The primary efficacy parameter is the sustained virologic response (SVR):
 - SVR is undetectable HCV RNA levels at the end of treatment and at Week 72

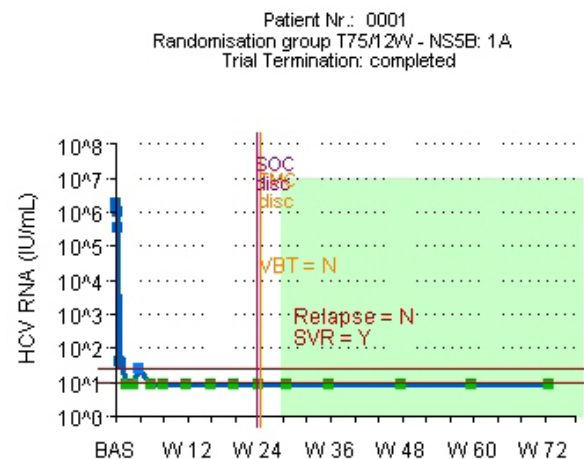
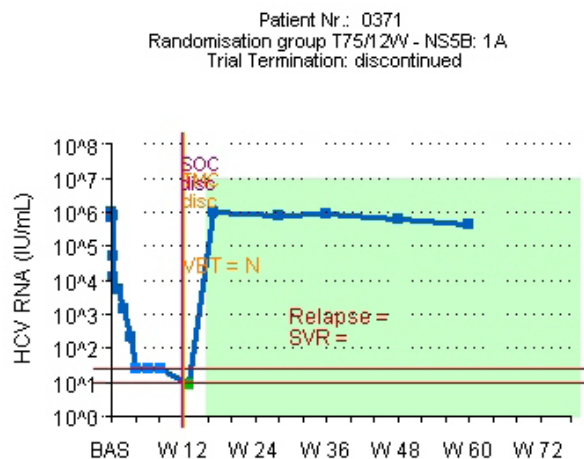
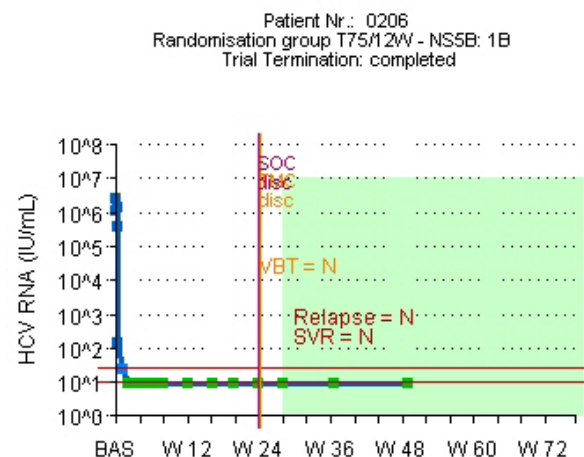
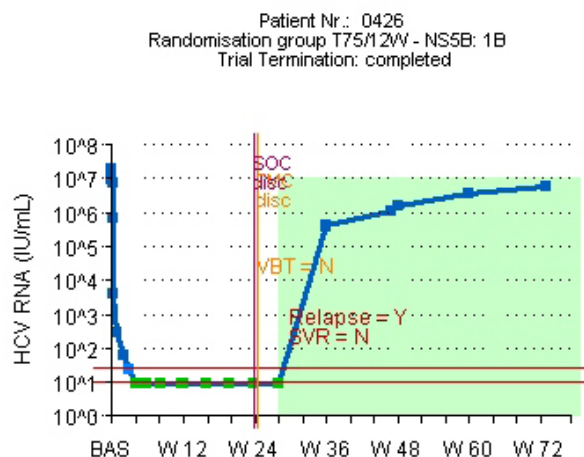
The HCV protease inhibitor trial: Non-responders



The HCV protease inhibitor trial: Responders



Individual profiles (Week 72)



Methods: The Semi-Parametric Mixed Effects Model

- Define the viral RNA for patient i at time t_{ij} as:

$$y_{ij} = g(t_{ij}) + \varepsilon_{ij}$$

- $g(t_{ij}) = (\beta_o + b_{oi}) + (\beta_1 + b_{1i})t_{ij} + \sum_{k=1}^K b_k(t_{ij} - k_k)_+^p$
- $k_1, \dots, k_K$ are a set of distinct knots in the range of t_{ij} , with $\mu_+ = \max(0, \mu)$
- The random specific intercept and slope $b_{oi}, b_{1i} : N(0, D)$, b_k is random effect associated with the smoother and assumed normally distributed and independent of b_{oi}, b_{1i} , that is, $b_k : N(0, \sigma_b^2)$, give SPMM with $\varepsilon : N(0, \sigma_\varepsilon^2)$.
- $Y = [y_{ij}]_{1 \leq i \leq n, 1 \leq j \leq m_i}$ (Durban et al., 2005) be the vector of stacked patient specific viral loads

Methods: The Semi-Parametric Mixed Effects Model

- $X = [1 t_{ij}]_{1 \leq i \leq n, 1 \leq j \leq m_i}$ the corresponding design matrix.
- $\beta = \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}$ the vector of fixed effects to be estimated.
- $Z_i = \left[(t_{ij} - k_k)_+^{\rho} \right]_{1 \leq j \leq m_i, 1 \leq k \leq K}$ is design matrix for the smoother.
- Analogous to the linear mixed model (Ruppert et al. 2003; Maringwa et al. 2008d):

$$Y = X\beta + Zb + \varepsilon$$

- As a consequence, the SPMM can be fitted using standard software for mixed models such as procedure MIXED in SAS®.

Methods: The Semi-Parametric Mixed Effects Model

- Model (1.1) is one in which the two groups differ in the linear part of the model but they share the same non parametric part.

$$g_{ij} = \begin{cases} (\hat{\beta}_0 + \hat{b}_{0i}) + (\hat{\beta}_1 + \hat{b}_{1i})t_{ij} + \sum_{k=1}^K b_k (t_{ij} - K_k)_+^2, & \text{if NR} \\ (\hat{\beta}_0 + \hat{\beta}_{01} + \hat{b}_{1i}) + (\hat{\beta}_1 + \hat{\beta}_{11} + \hat{b}_{1i})t_{ij} + \sum_{k=1}^K b_k (t_{ij} - K_2)_+^2, & \text{if R} \end{cases}$$

- The truncated basis ($\phi = 2$) implies that the smoother will fit peaks and valleys more closely than a linear truncated basis (Ruppert et al. 2003).

Methods: The Semi-Parametric Mixed Effects Model

- The rate of viral decline becomes:

$$g_{ij} = \begin{cases} (\hat{\beta}_0 + \hat{b}_{0i}) + \frac{d}{dt} + \sum_{k=1}^K b_k (t_{ij} - k_k)_+^2, & \text{for NR} \\ (\hat{\beta}_1 + \hat{\beta}_{11} + \hat{b}_{1i}) \frac{d}{dt} + \sum_{k=1}^K b_k (t_{ij} - k_k)_+^2, & \text{for R} \end{cases}$$

Application of (1.1) in SAS®

- The mean structure for the fixed effects component of the model can be specified by:

MODEL VLLOGRES = Time SVR Time*SVR/ NOINT SOLUTION

Methods: The Semi-Parametric Mixed Effects Model

- The model has two random components. The first random component accounts for subject heterogeneity.

`random intercept Time / subject = usubjid ;`

- The second random component specifies the design matrix for the smoother. Z1-Z13 below are the columns of the design matrix Z.

`random z1-z13 / type=toep(1) solution;`

- Note that the option " `type = toep(1)`" specifies the covariance matrix of the random effect b_k which has a K x K diagonal Toeplitz structure of the form $\sigma_b^2 I_{k \times k}$.

Methods: The Semi-Parametric Mixed Effects Model

- The complete code is given:

```
proc mixed data=datasw12 method=ml order=data asycov  
covtest;  
class svr usubjid ;  
model vlogres= Time svr Time*svr/ noint solution  
outp=predspw12(rename=(pred=vlspw12)) ;  
random z1-z13 / type=toep(1) ■ solution;  
random intercept Time / subject= usubjid ;  
Ods output covparms =cpspw12;  
Ods output solutionR =randefsw12;  
Ods output solutionF =fixefspw12;  
run;
```

Methods: The Semi-Parametric Mixed Effects Model

- Model (1.2) separate curves smoothed separately with the same smoothing parameter for the two groups. This is done by specifying a group specific design matrix for the random effects of the smoother $\hat{b}_k$.

$$\hat{g}_{ij} = \begin{cases} (\hat{\beta}_0 + \hat{b}_{0i}) + (\hat{\beta}_1 + \hat{b}_{1i})t_{ij} + \sum_{k=1}^K \hat{b}_k^{NR}(t_{ij} - k_k)_+^2, & \text{for NR} \\ (\hat{\beta}_0 + \hat{\beta}_{01} + \hat{b}_{0i}) + (\hat{\beta}_1 + \hat{\beta}_{11} + \hat{b}_{1i})t_{ij} + \sum_{k=1}^K \hat{b}_k^R(t_{ij} - k_k)_+^2, & \text{for R} \end{cases}$$

- $\text{var}(\hat{b}_k^{NR}) = \text{var}(\hat{b}_k^R) = \sigma_b^2$
- Again, the rate of viral decline can be obtained as in (1.1)

Methods: The Semi-Parametric Mixed Effects Model

Application of (1.2) in SAS®

- Includes group specific smoother by changing the covariance matrix of the random effects for the smoother. This implies that two sets of random effects for the smoother will be estimated.

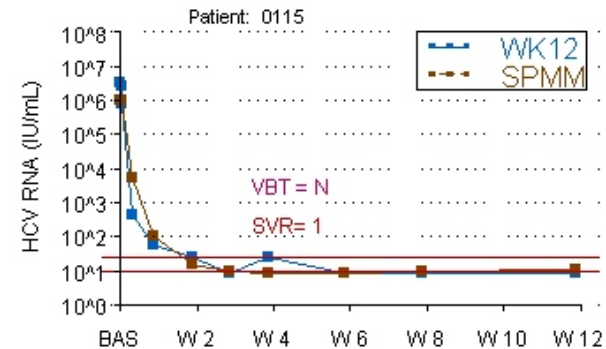
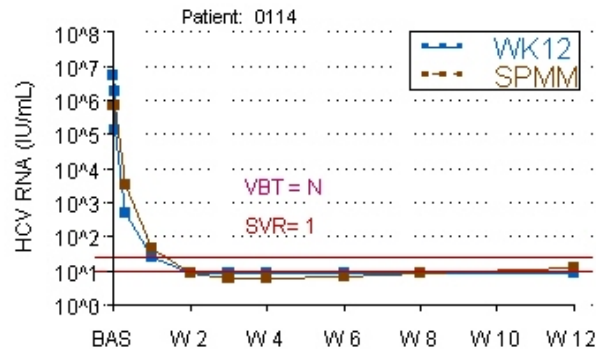
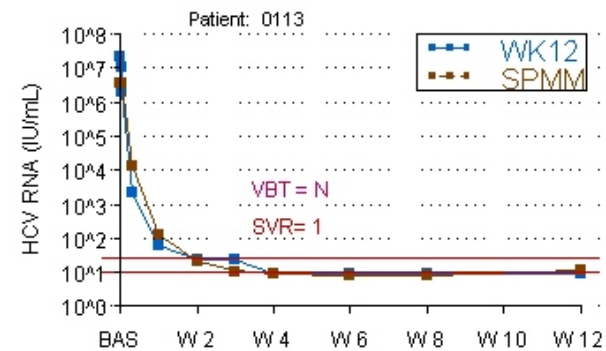
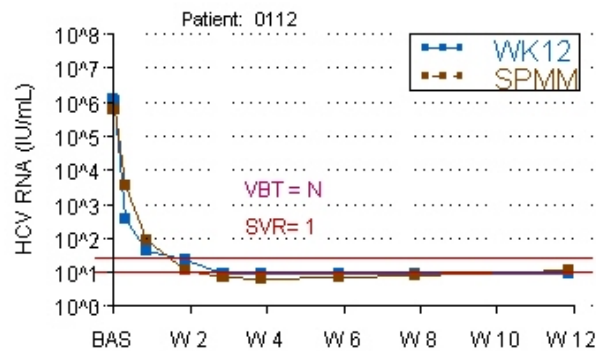
random z1-z13 / type=toep(1) **subject=SVR** solution;

- Model (1.3): model with subject specific smoothers but with the same smoothing parameter.

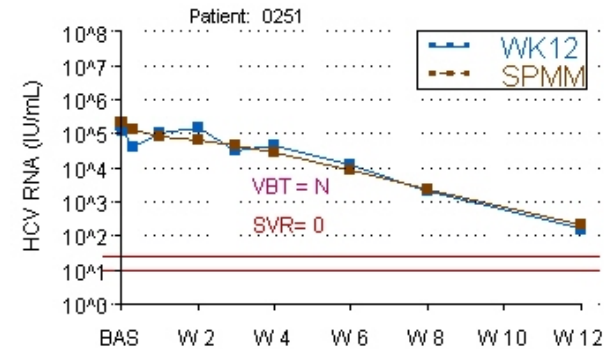
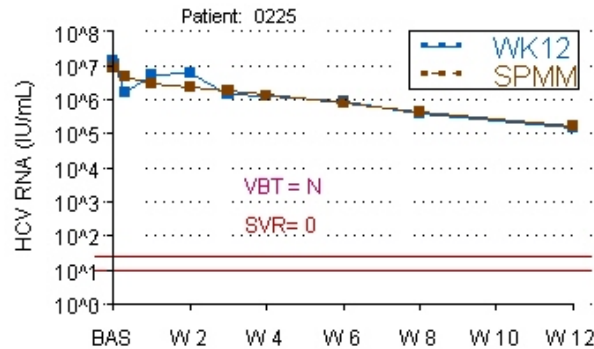
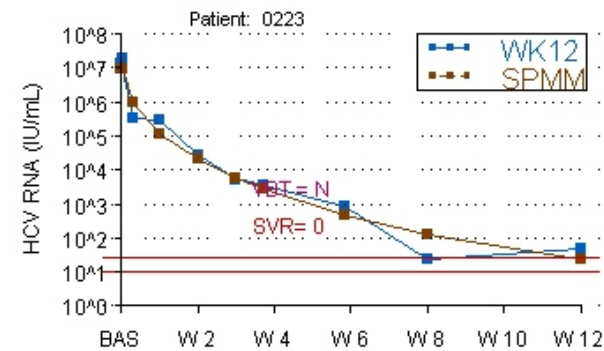
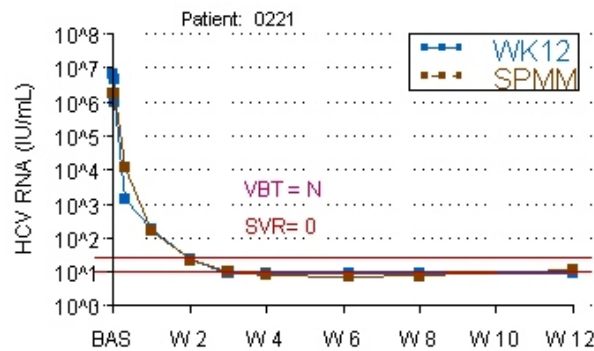
$$\hat{g}_{ij} = \begin{cases} (\hat{\beta}_0 + \hat{b}_{0i}) + (\hat{\beta}_1 + \hat{b}_{1i})t_{ij} + \sum_{k=1}^K \hat{b}_{ki}(t_{ij} - k_k)_+^2, & \text{for NR} \\ (\hat{\beta}_0 + \hat{\beta}_{01} + \hat{b}_{0i}) + (\hat{\beta} + \hat{\beta}_{11} + \hat{b}_{1i})t_{ij} + \sum_{k=1}^K \hat{b}_{ki}(t_{ij} - k_k)_+^2, & \text{for R} \end{cases}$$

The rate of decline is obtained in a similar way as in (1.1)

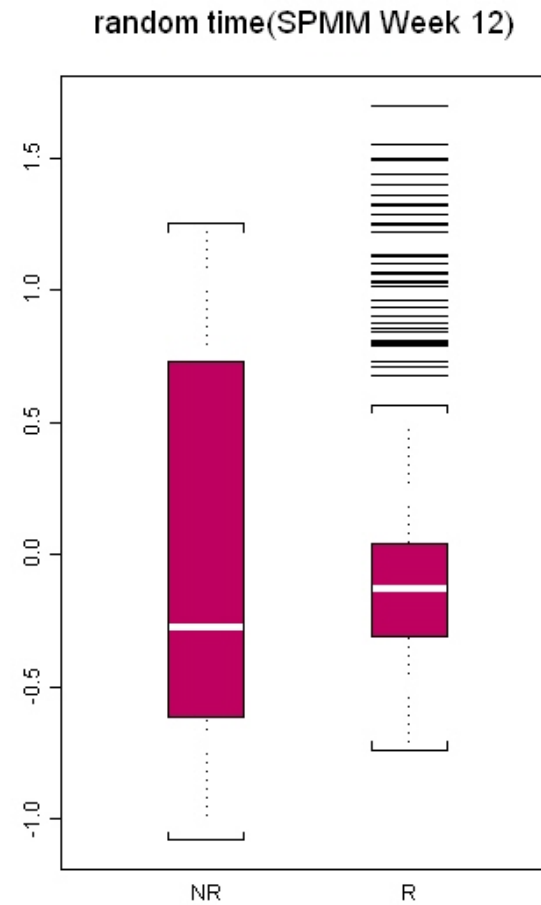
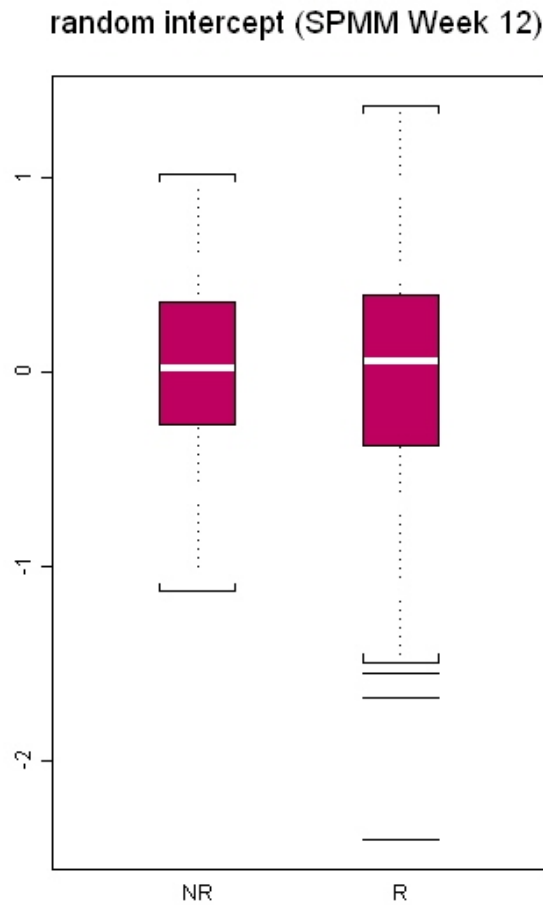
Results: Observed and Fitted data (SVR= 1)



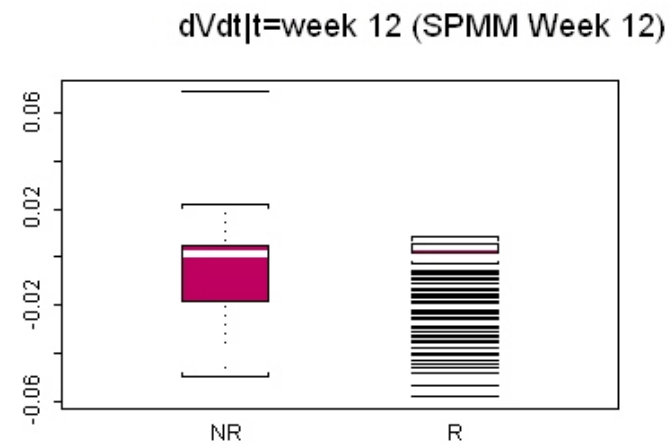
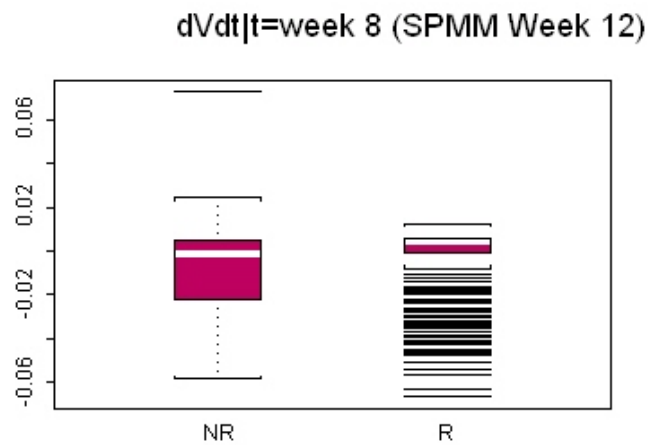
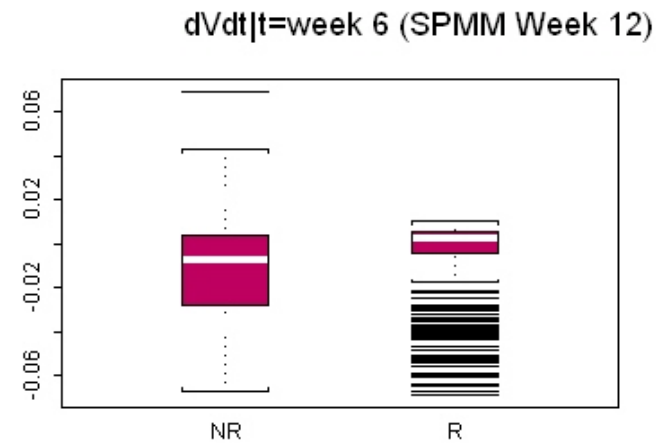
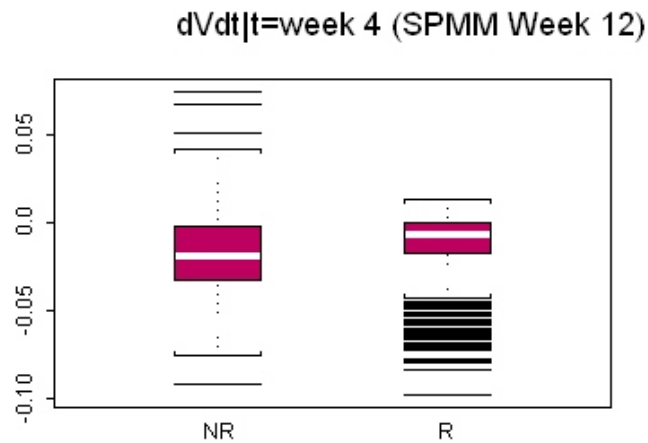
Results: Observed and Fitted data (SVR= 0)



Results: Inference for the random effects



Results: Inference for the rate of viral decline



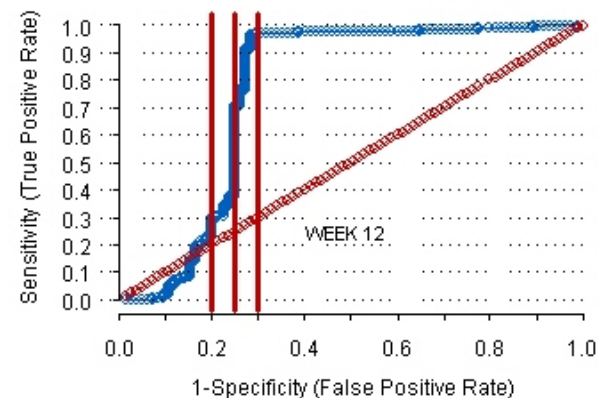
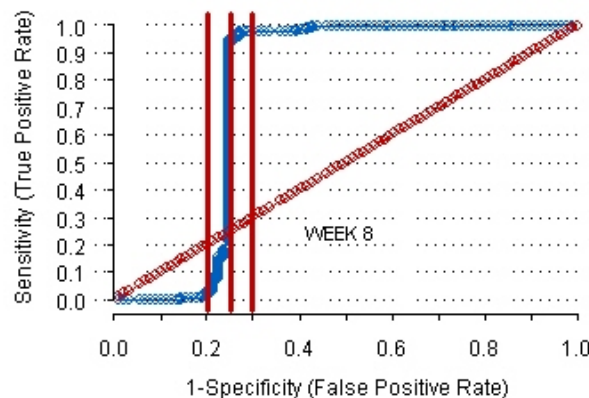
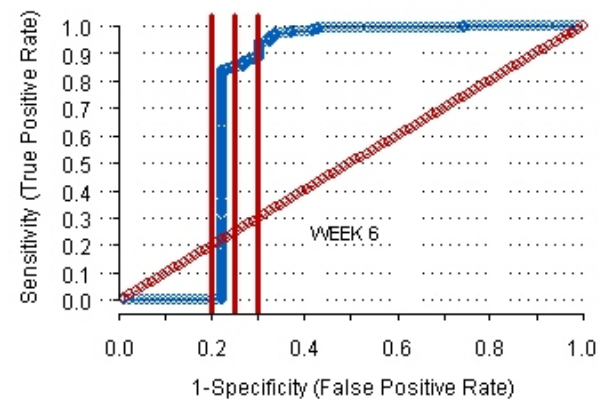
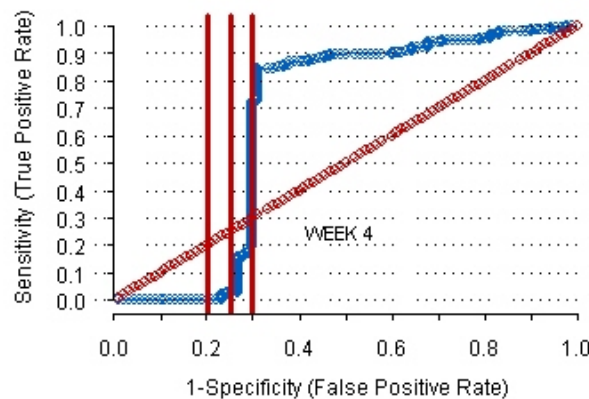
Prediction of SVR using the logistic regression

- Let

$$R_i = \begin{cases} \text{responder(R)}, & \text{if SVR}=1 \\ \text{non-responder(NR)}, & \text{if SVR}=0 \end{cases}$$

- Aim is to model the probability to be a responder as a function of the subject specific parameters.
- $p = P[R_i = 1 | \hat{g}'(t = k), \hat{b}_{0i}]$ given the viral characteristics.
- Using logit link, $\log\left(\frac{p}{1-p}\right) = \alpha + \beta x$; and, $p = \frac{\exp(\alpha + \beta x)}{1 + \exp(\alpha + \beta x)}$
- We fitted logistic regression models for SVR as a function of the rate of viral change and random intercept at different time points

Results: Prediction of sustained virologic response



Conclusions

- This era of HCV treatment using a triple therapy of Direct Antiviral (DA), PegIFN and RBV leads to rapid wild-type viral decline but also to development of resistant mutations.
- Typically in HCV trials, patients receive 24/48 weeks of treatment and are then followed up for 24 weeks before assessing the primary efficacy endpoint.
- Throughout the duration of the study, HCV viral RNA is continually evaluated resulting in longitudinal measurements.
- The evolution of viral profiles over time was studied via semi-parametric mixed effects models.

Conclusions

- It is observed that sustained virologic response at week 24 (SVR24) post treatment is strongly correlated with early viral activities of the patients at treatment week 12.
- The model for the prediction of SVR based on the viral information at week 12 is over 90% sensitive and near 80% specific.
- We conclude that individual level surrogacy based on week 12 viral profile to predict the outcome of interest is possible.
- However, surrogate extrapolation to a new treatment (mechanism) is a subject of further research among the clinical team.

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