Modelling and simulation of neurological endpoints to aid clinical trial design in intracerebral hemorrhage

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Clinical background and stroke trials

- Strokes can be produced either by blood clots or by bleeding
- Intracerebral hemorrhage (stroke by bleeding) currently has no effective treatment and is often fatal
- Treatment perspectives aim at reducing bleeding (by inducing coagulation) but a recent large trial has proven ineffective*
- Trial outcome is currently measured by the 0-6 point categorical modified Rankin Scale (mRS) after 90 days
- Can we make earlier trials more powerful…?
  - incorporate multiple mRS assessments?
  - include alternative stroke scale measurements (NIHSS)?
  - …so we can determine if running a large trial is worthwhile

*Phase III NovoSeven recombinant activated factor VII (rFVIIa) trial in hemorrhagic stroke patients: Mayer SA, Brun NC, Begtrup K, et al. Efficacy and Safety of recombinant Activated Factor VII for Acute Intracerebral Hemorrhage. N Engl J Med 2008;358:2127-37.

Modified Rankin Scale vs National Institute of Health Stroke Scale

	mRS
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

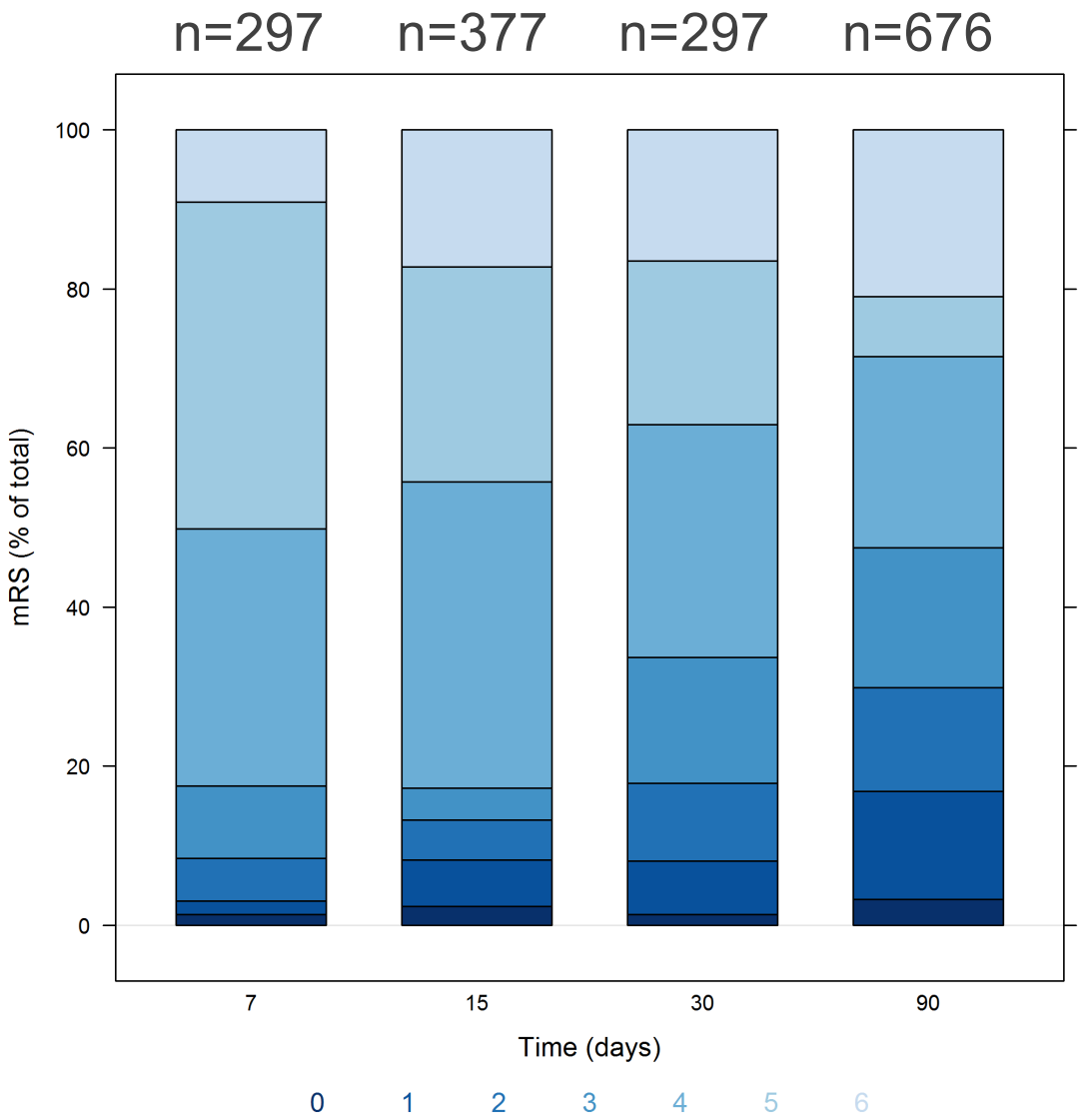
	NIHSS
0	No Stroke Symptoms
1-4	Minor Stroke
5-15	Moderate Stroke
16-20	Moderate to Severe Stroke
21-42	Severe Stroke

Model background and structure

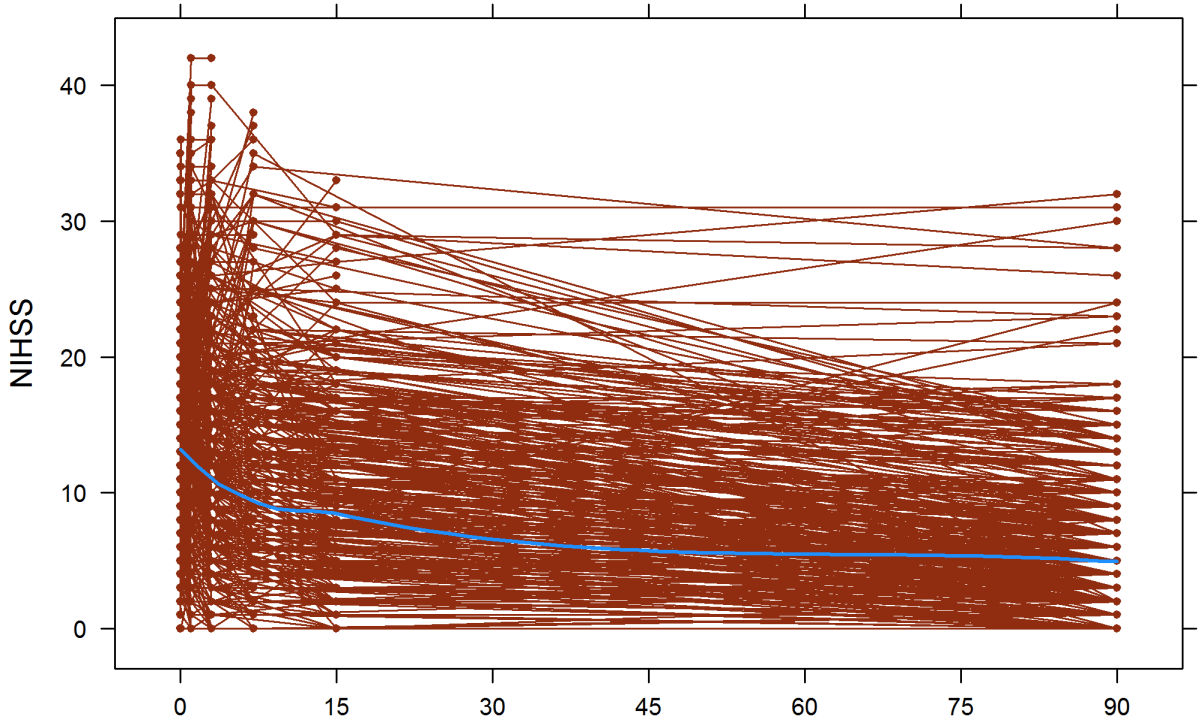
- Aim is to provide longitudinal models for mRS and NIHSS including a component where drug action may be incorporated
- By combining mRS and NIHSS information including the time profile, a potentially more powerful analysis method should be possible
- Available data: VISTA-ICH database* with placebo-arm data
- Assumed method of action:
  - patients enter the clinic after a hemorraghic stroke
  - if the drug stops further bleeding, outcome should improve
- Current presentation is *Work in Progress*

*VISTA: The Virtual International Stroke Trials Archive at http://www.vista.gla.ac.uk/

Observed distribution of cumulative mRS scores across trials by time



Time profiles of National Institute of Health Stroke Scale (NIHSS): 0-42 point scale

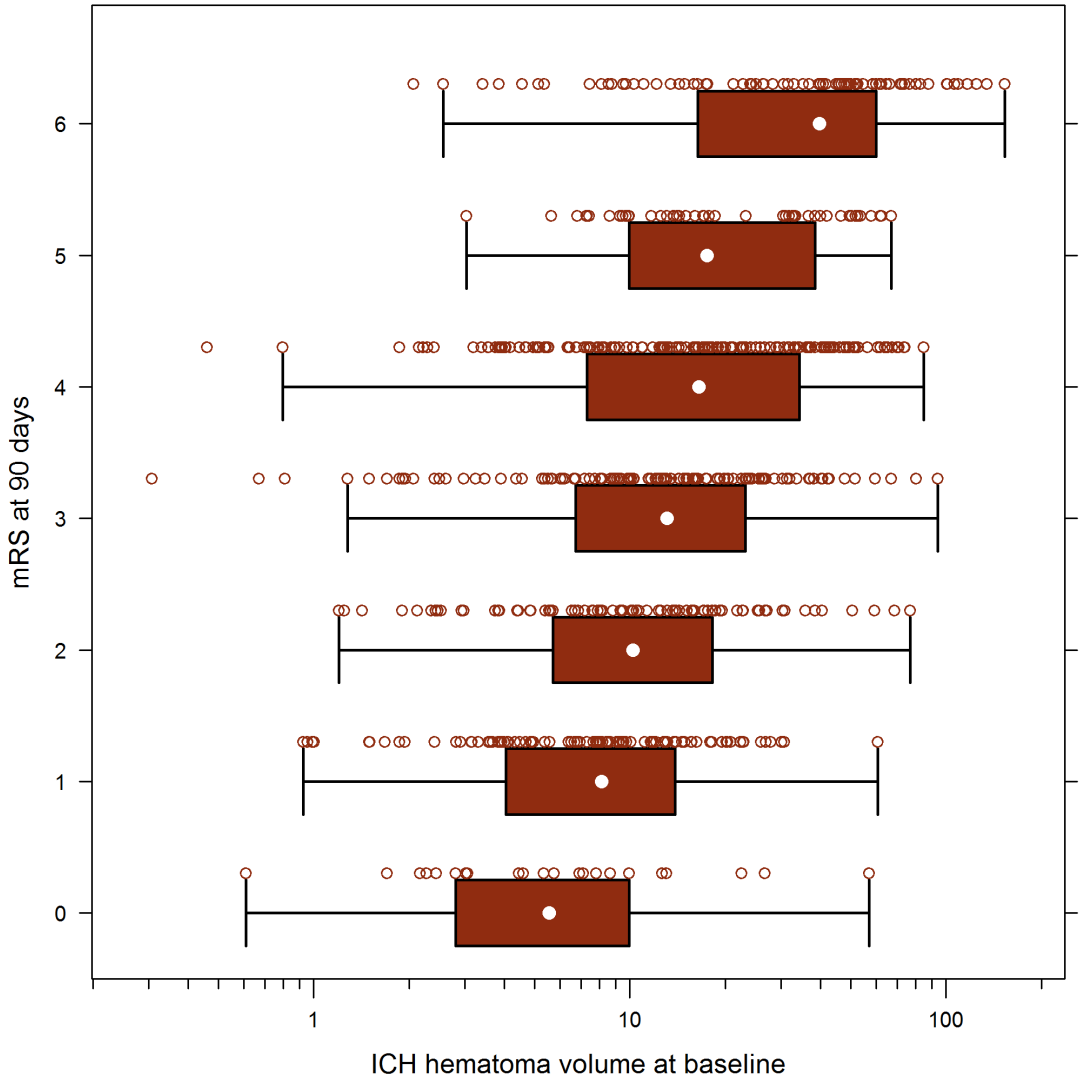


Much more fine-grained info at the start

Factors that influence outcome:

1. ICH log hematoma volume at baseline *vs.* mRS scores at day 90

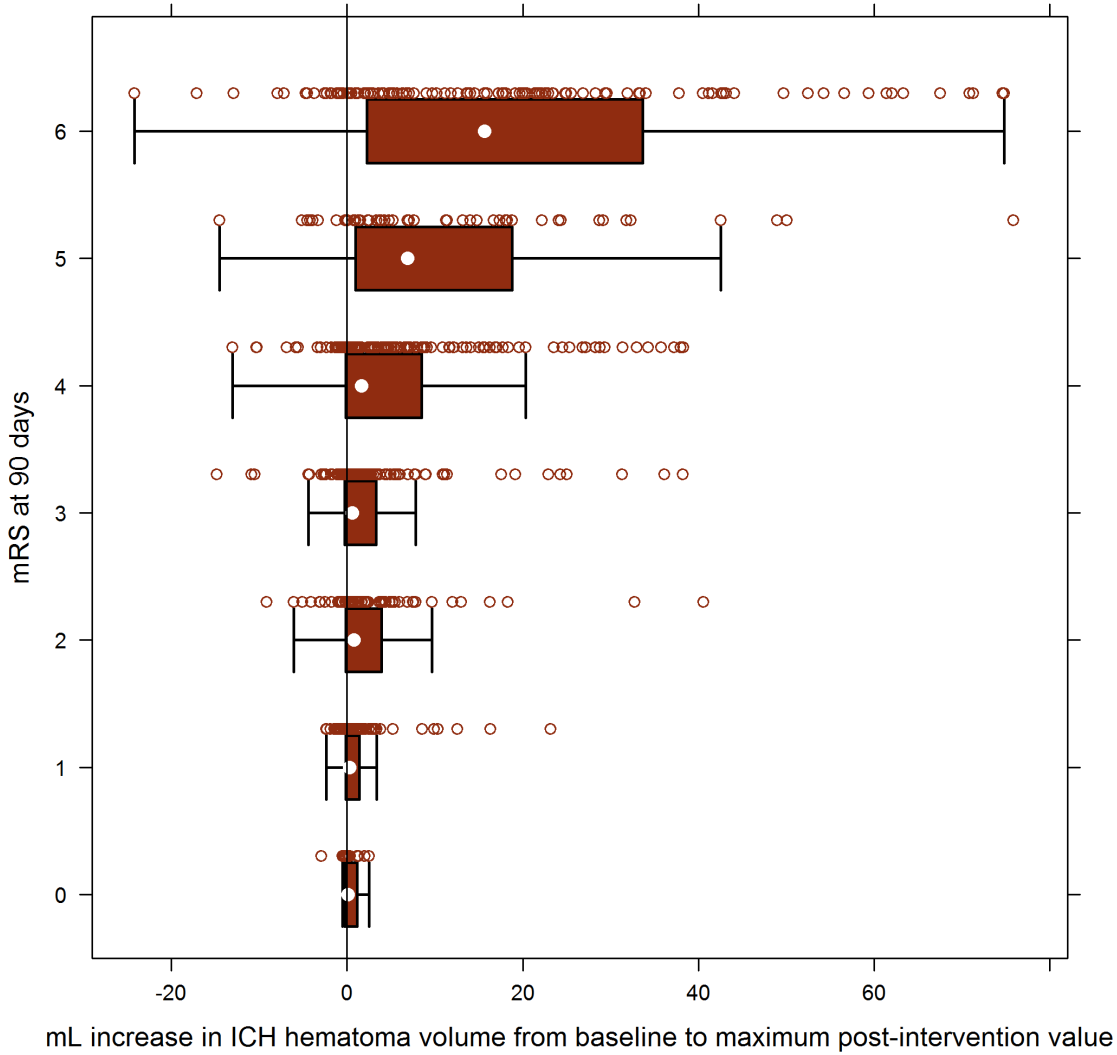
Box plots and individual values



Factors that influence outcome:

2. Absolute change in hematoma volume (mL) *vs.* mRS scores at day 90

Box plots and individual values

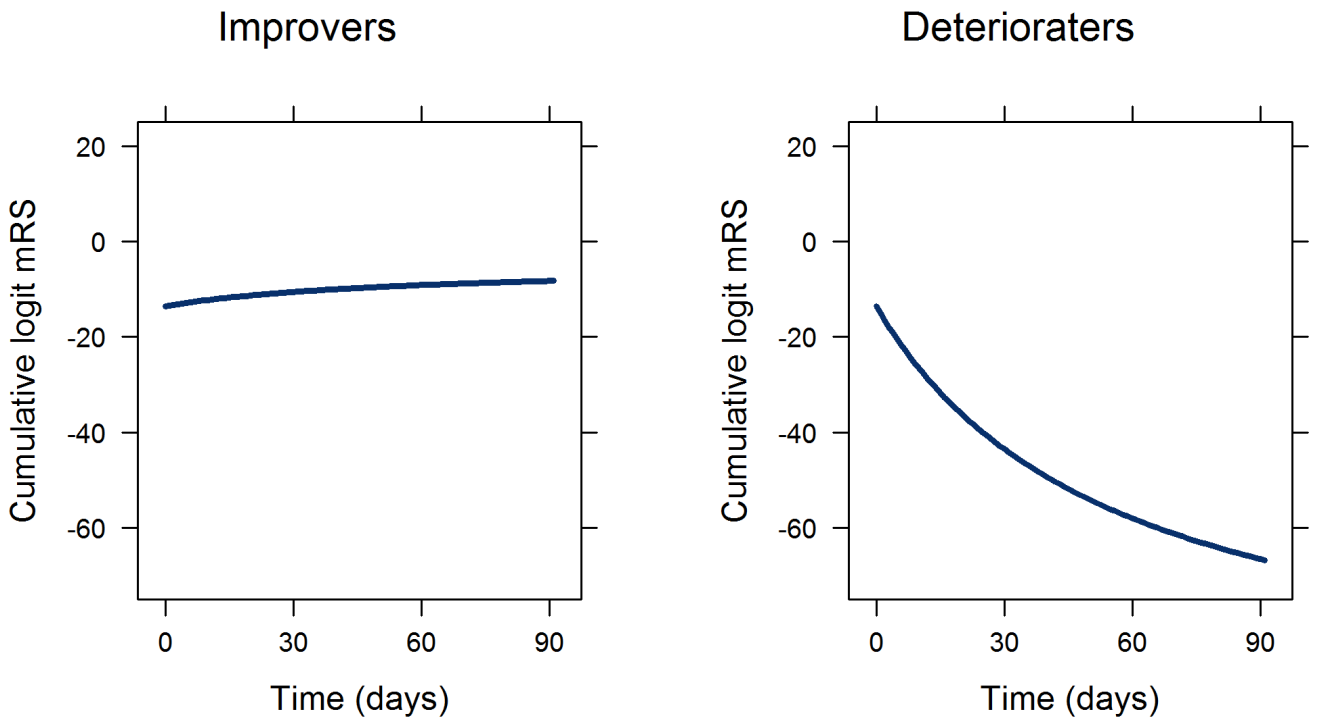


Longitudinal model for mRS

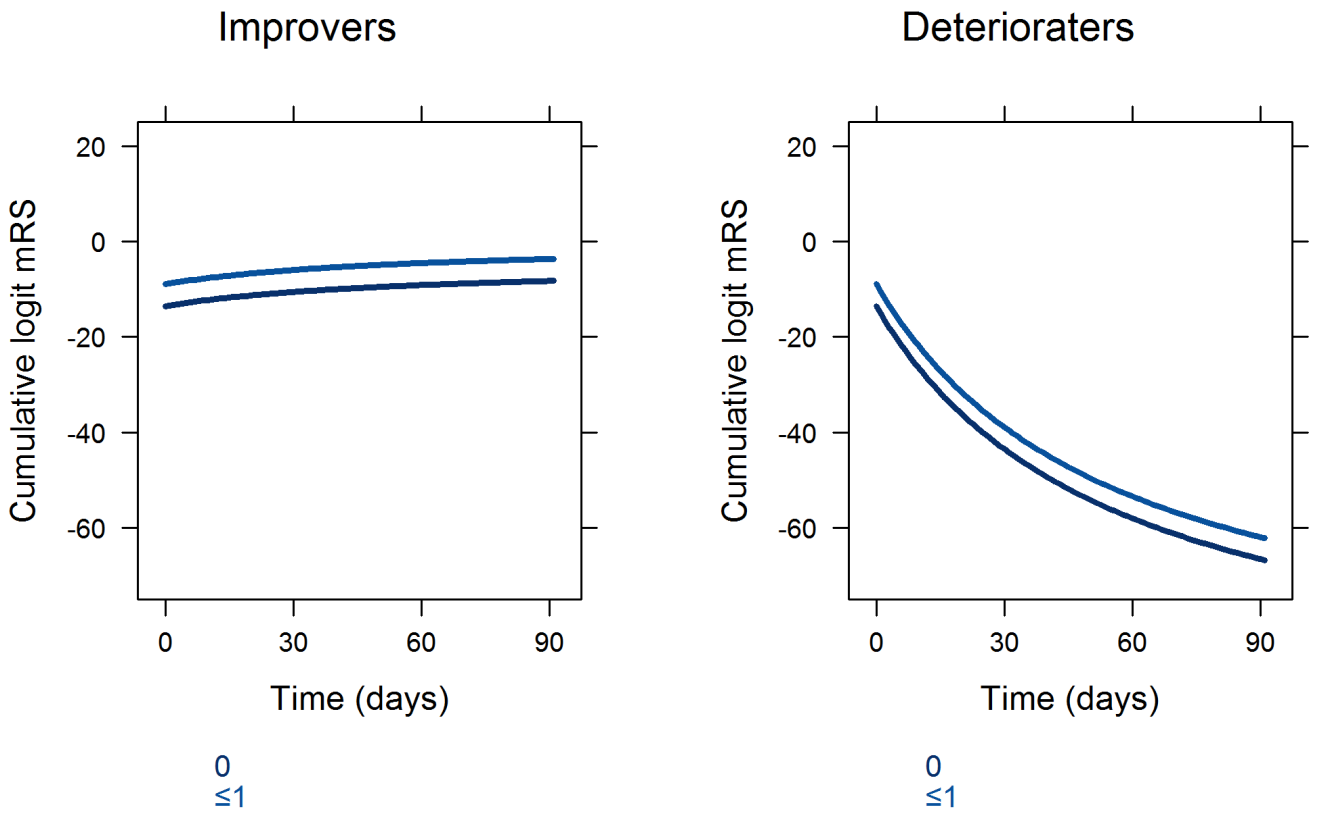
- mRS is a 0-6 point scale
- Ordered categorical model
- Fraction of subjects is estimated with an mRS score of 0, ≤1, ≤2, ≤3, ≤4, ≤5 (everyone has a score ≤6)

- Mixture model where NONMEM separates improving and deteriorating subjects
- Underlying E_{max}-type time profile
  - Positive E_{max}: larger probability of a good outcome: improvers
  - Negative E_{max}: deteriorators

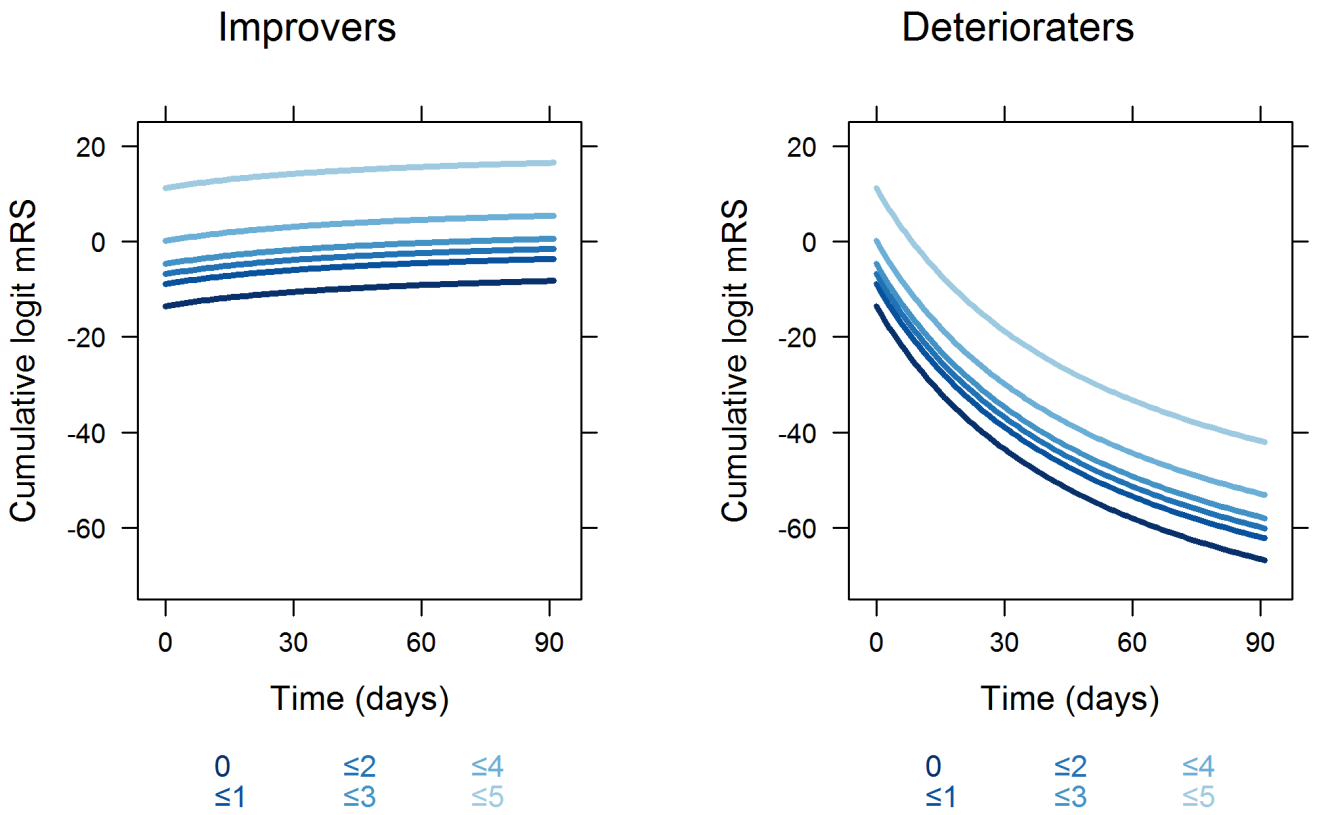
Time profiles for the population value of the logits for mRS = 0



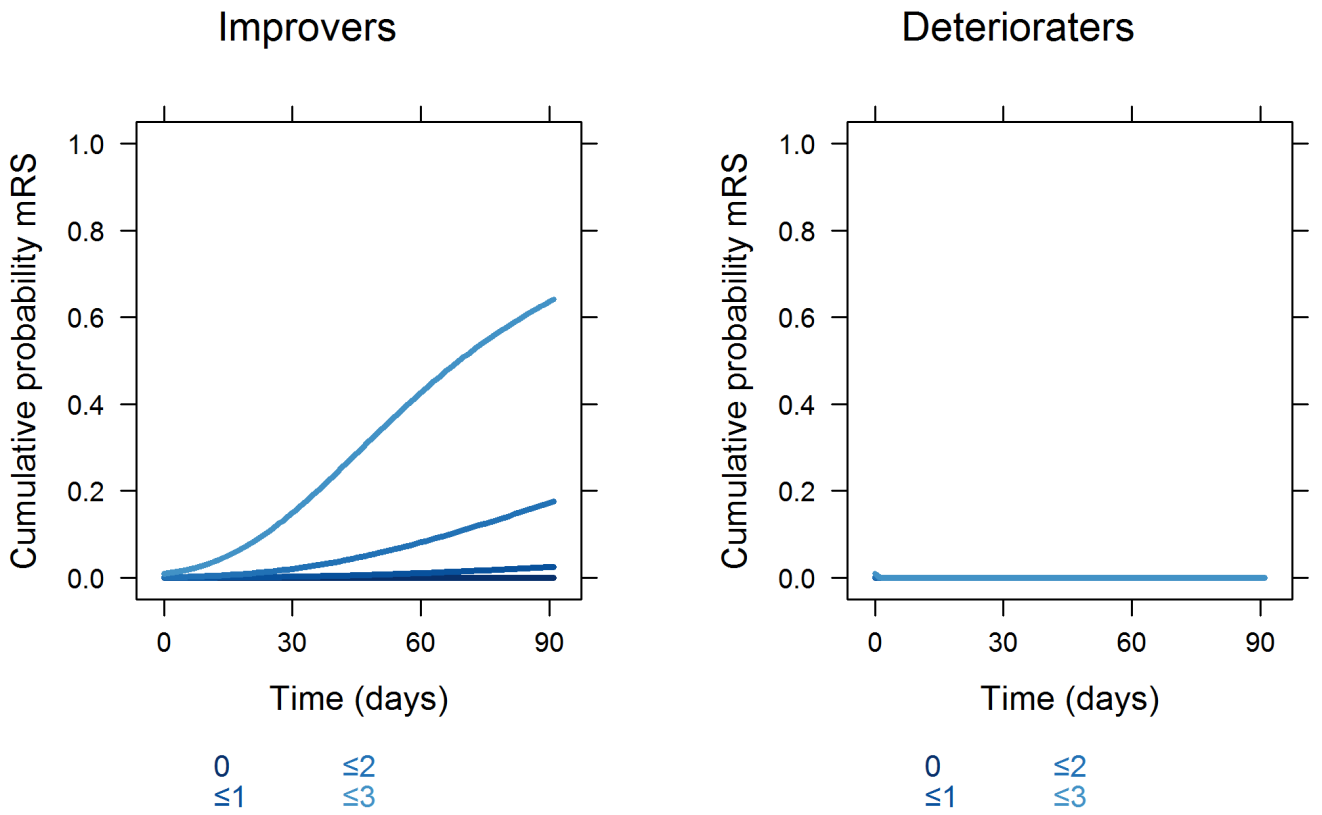
...with a parallel shift for scores ≤1...



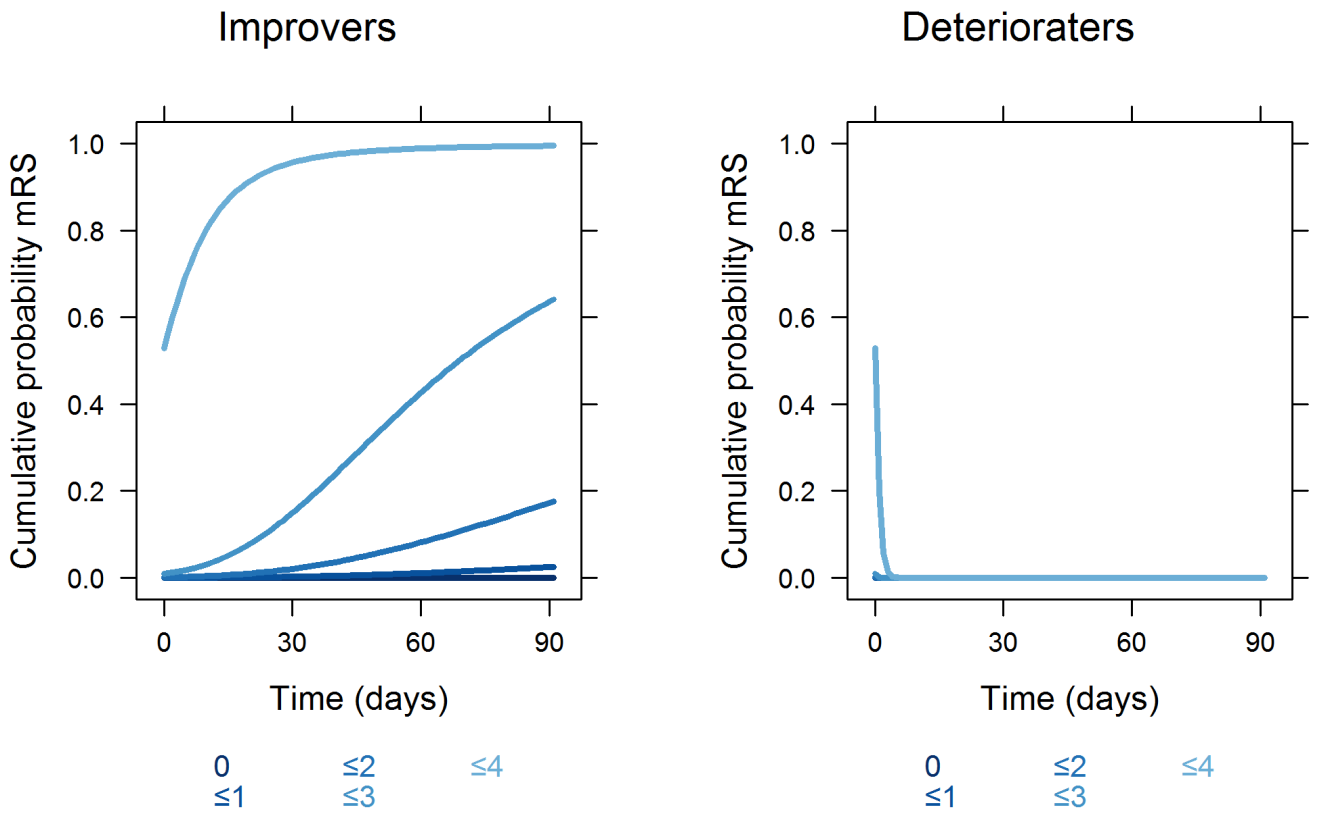
...and subsequent cumulative scores



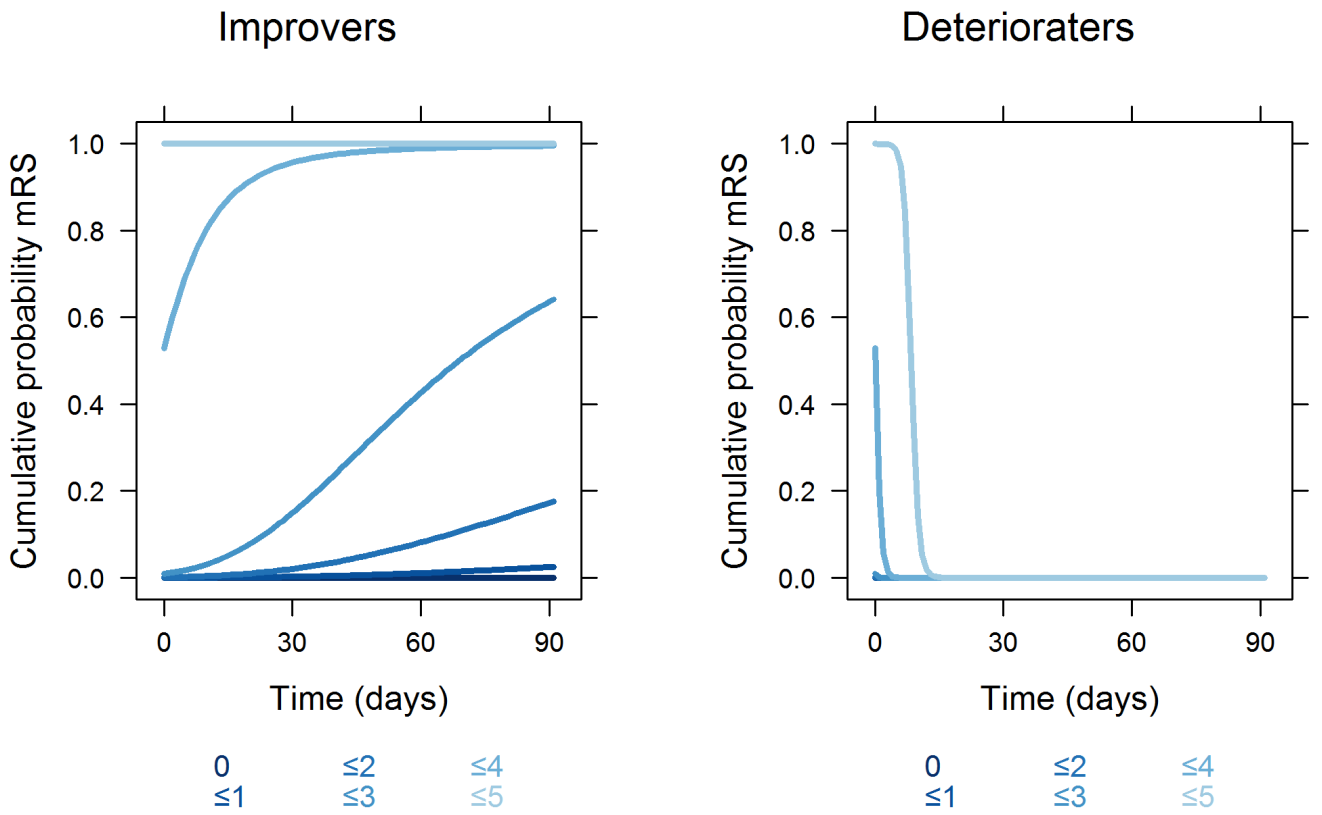
...with corresponding probabilities



...with corresponding probabilities



...with corresponding probabilities

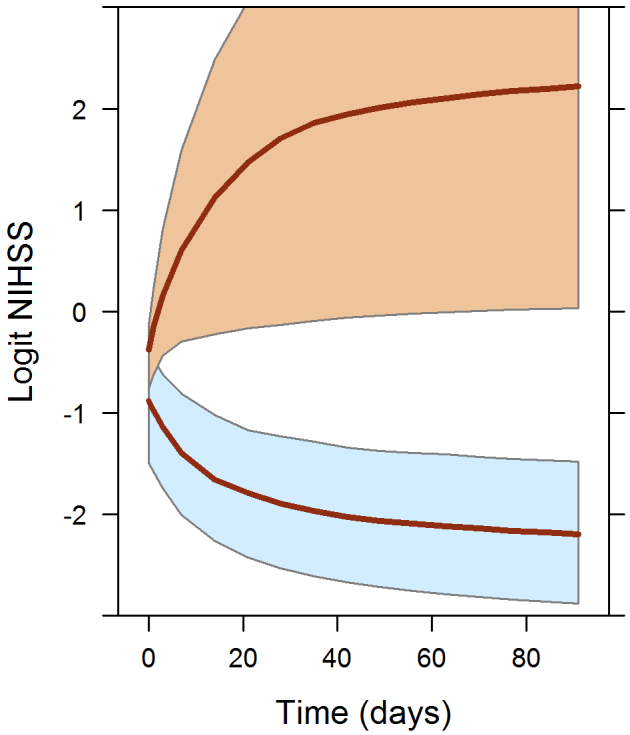


Longitudinal model for NIHSS

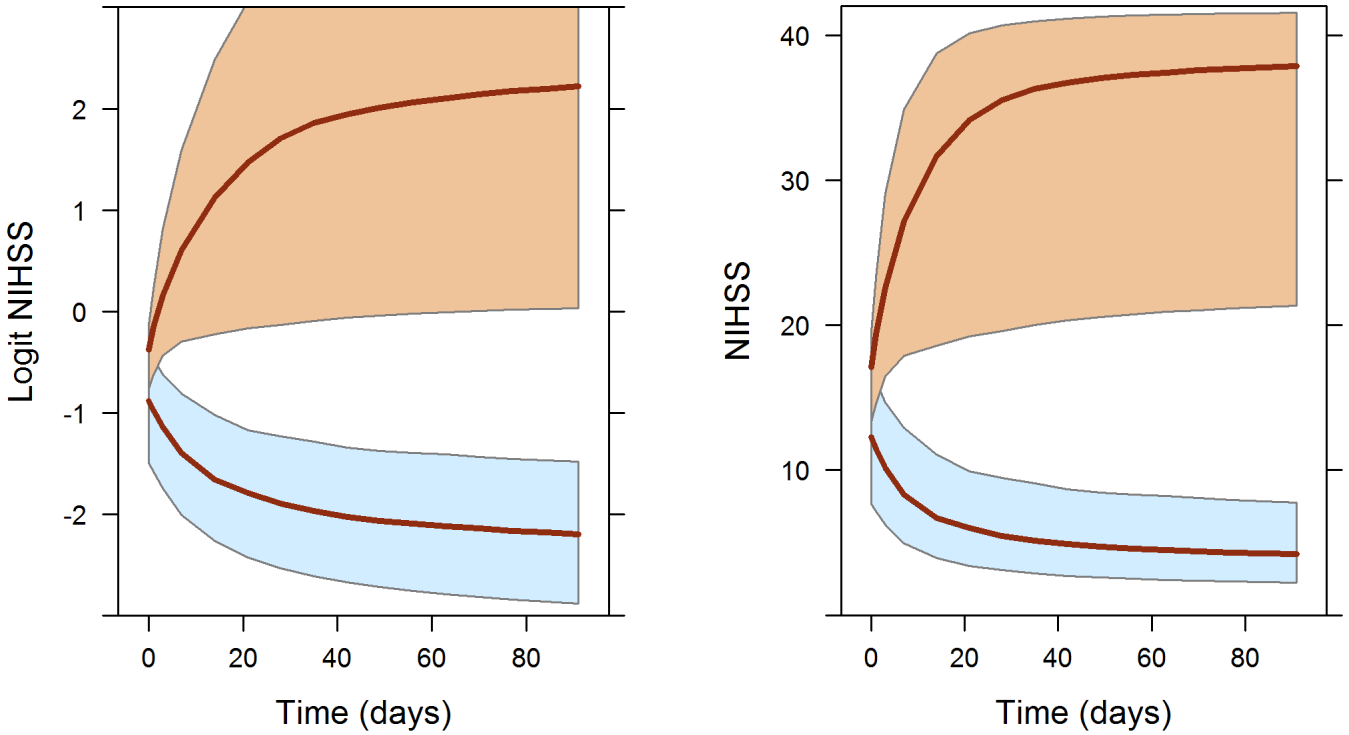
- NIHSS is a 0-42 point scale
- Continuous model with boundaries imposed (0 and 42) using a logistic transformation
- Again: underlying E_{max}-type time profile, and a mixture model where NONMEM separates improving and deteriorating subjects

The same time profile as for mRS is used to drive the NIHSS on a logit scale: deterioraters now go up instead of down...

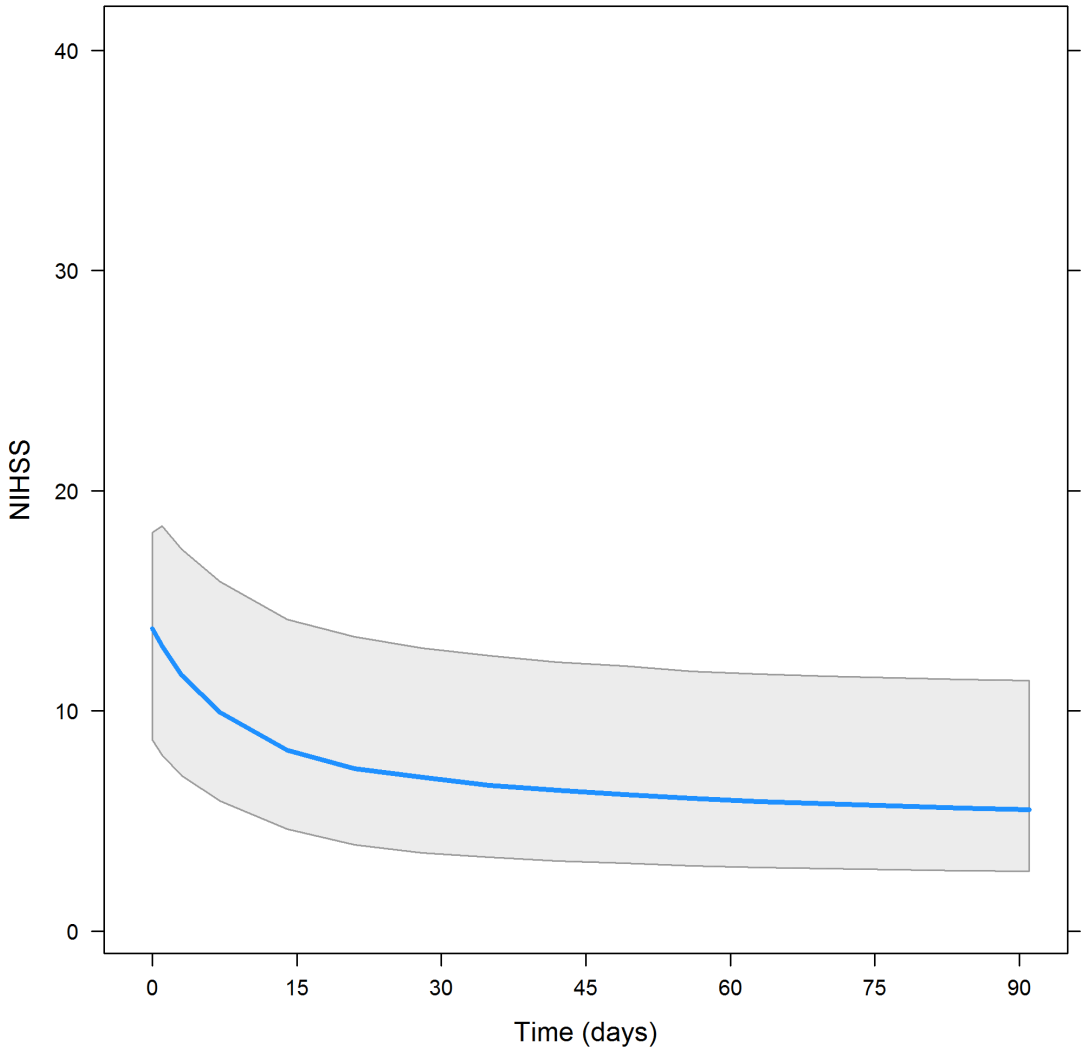
50% of the profiles for improvers (blue), deterioraters (orange)



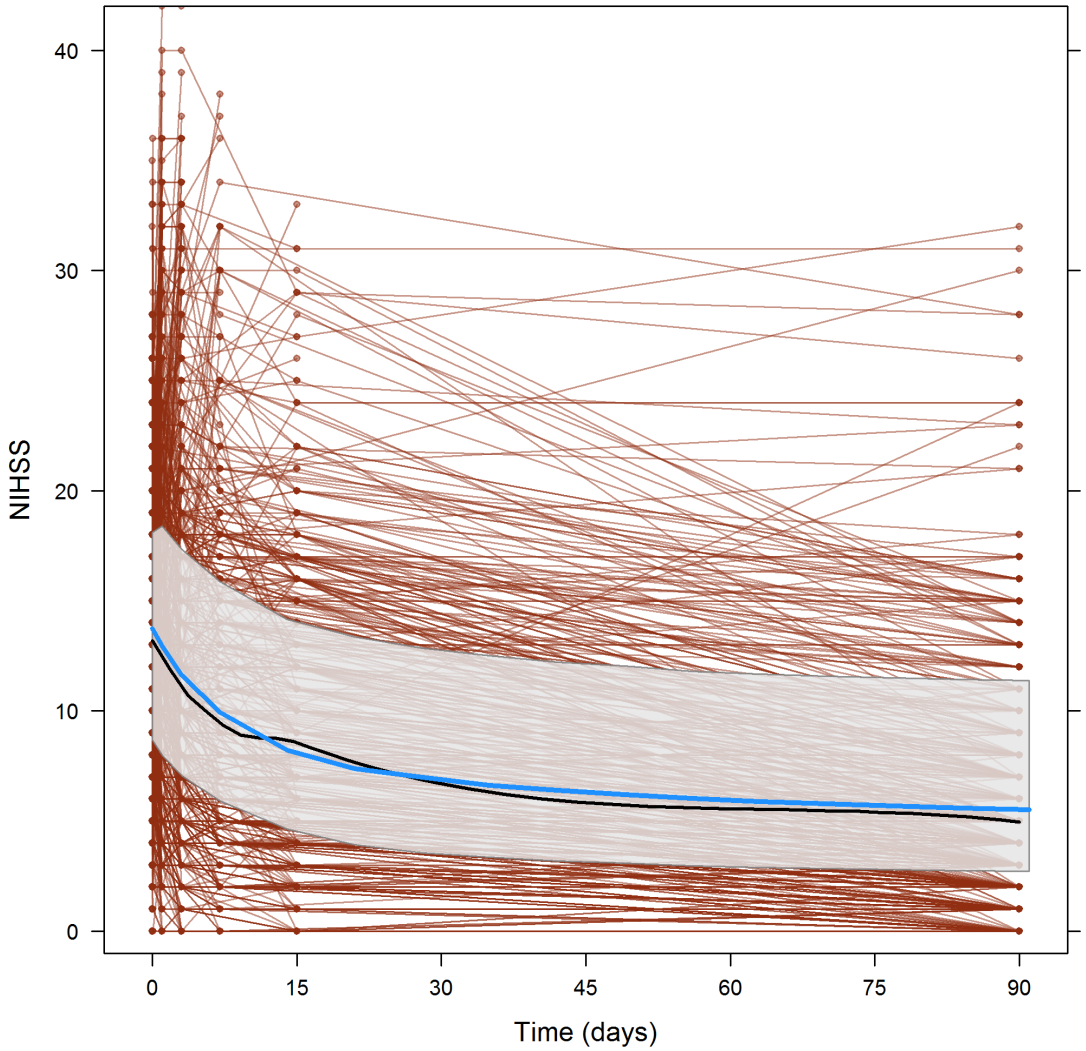
...which can be translated back to the original 0-42 point scale



...with the following combined profile across the two populations



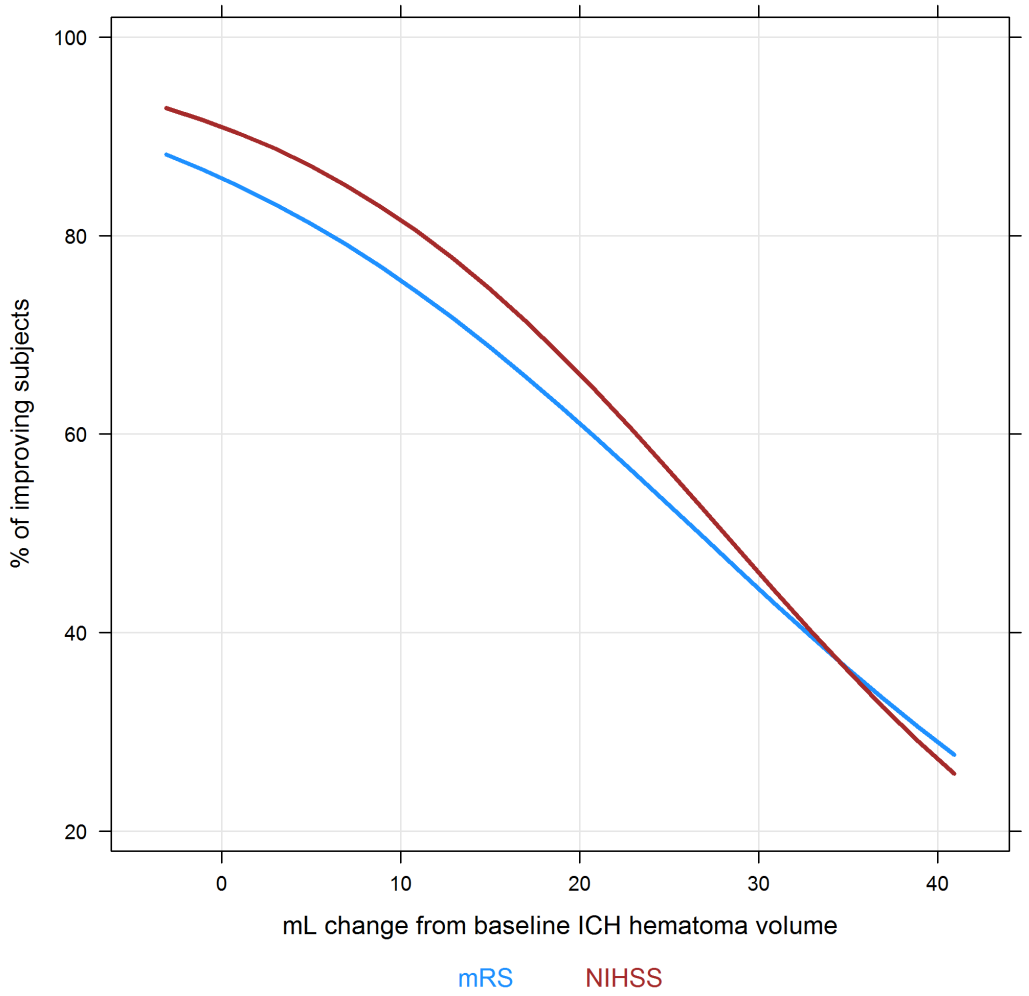
...and with the raw-data individual profiles and a loess smooth superimposed (black line)



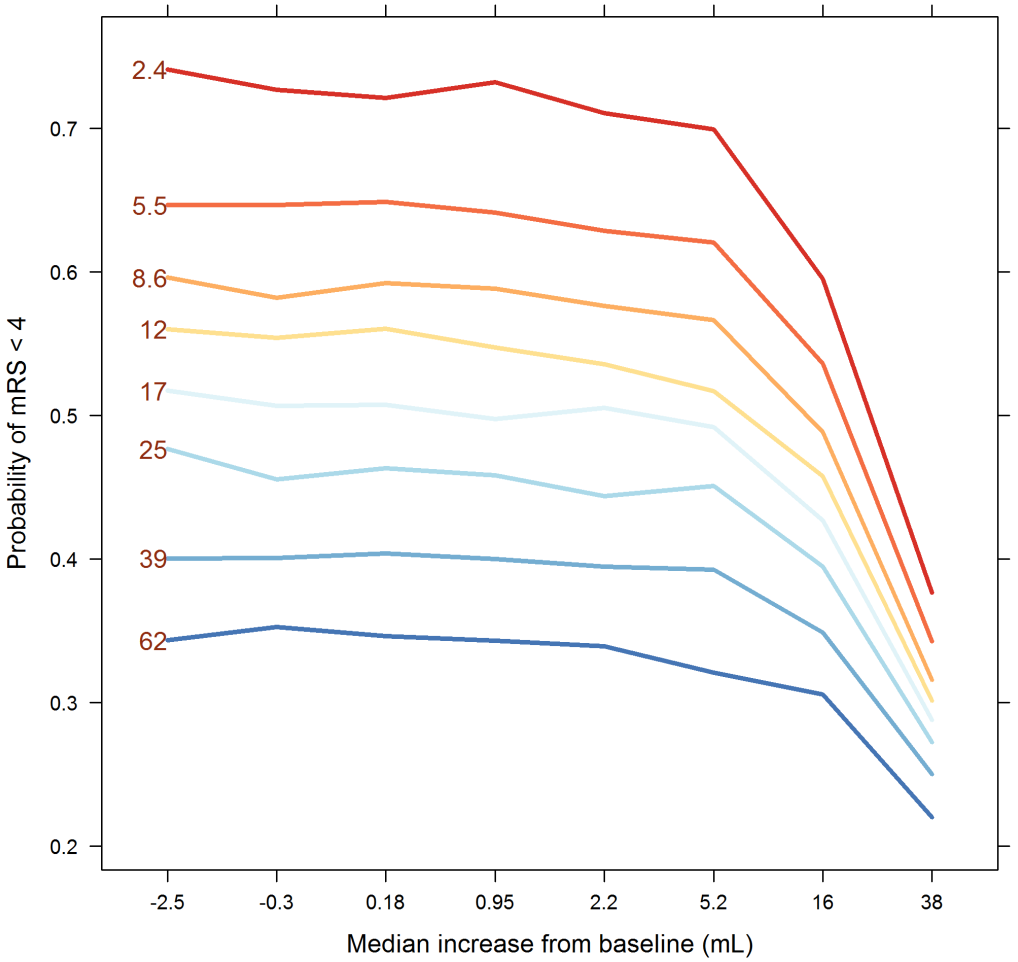
Covariate effects

- Covariates are modelled to affect the mRS and NIHSS profile either at baseline, or on fraction of improving patients:
  - Hematoma volume at baseline affects mRS and NIHSS at baseline
  - Change in hematoma volume affects the fraction of improving subjects

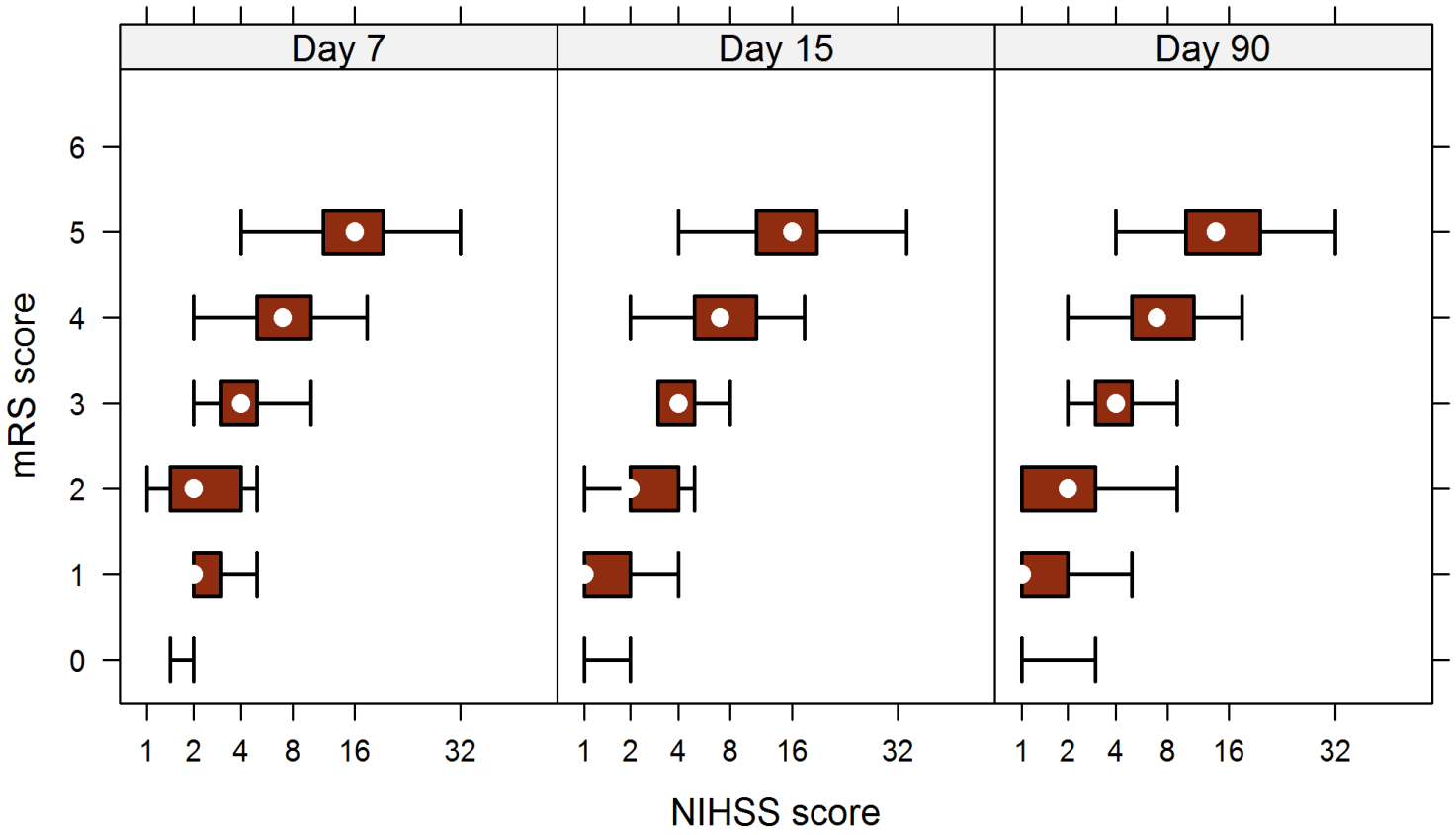
Initially separate models for mRS and NIHSS Similar effect of change in hematoma volume on % improving subjects for mRS and NIHSS



The model can be used to predict the probability of an mRS score <4 at the different combinations of baseline volume (lines) and volume increase, at day 90

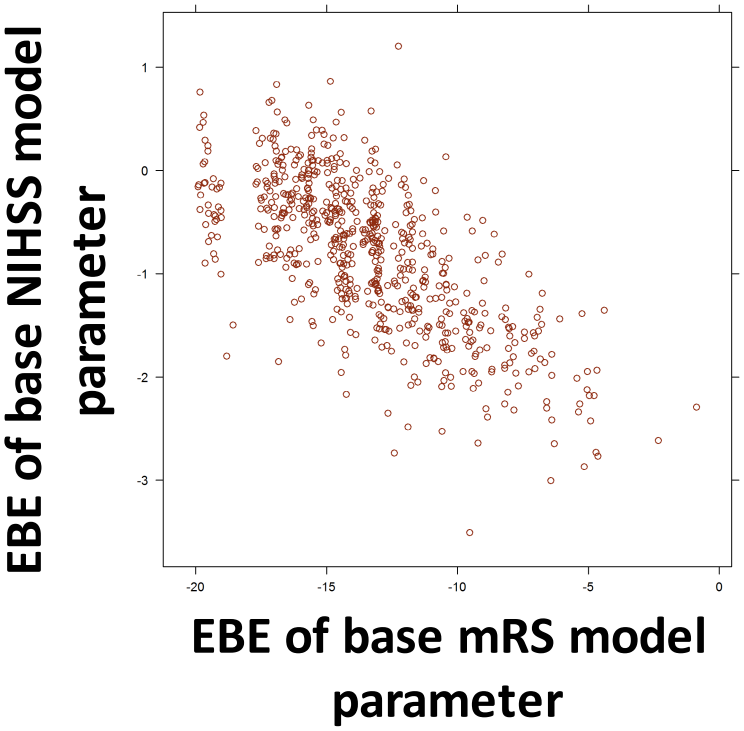


Strong correlation between mRS and NIHSS scores allows a combined mRS/NIHSS model

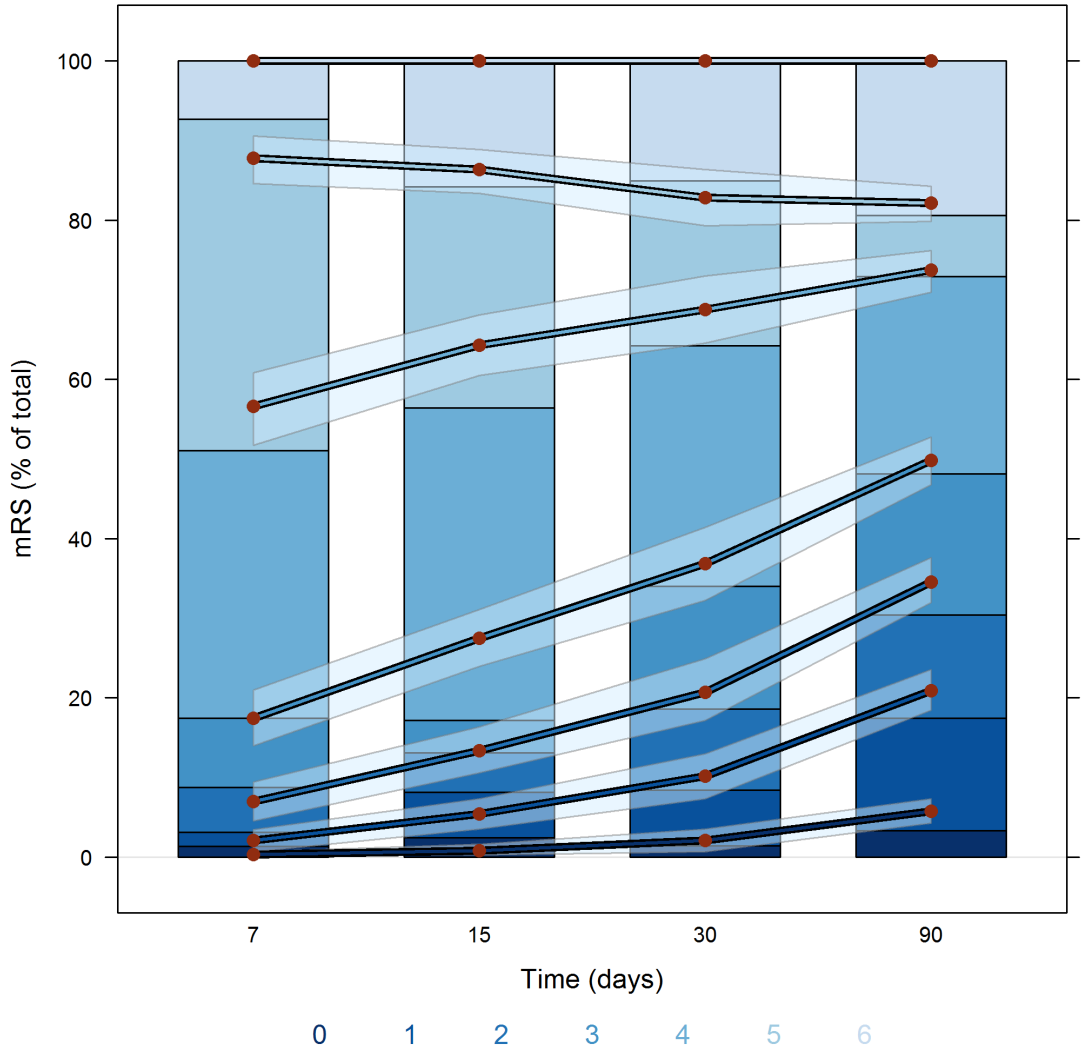


Final combined mRS/NIHSS model

- The improving and deteriorating populations are the same for mRS and NIHSS
- The maximum change from baseline for a subject has a near perfect correlation between mRS and NIHSS
- Base model parameters are highly correlated for mRS and NIHSS (-0.822)

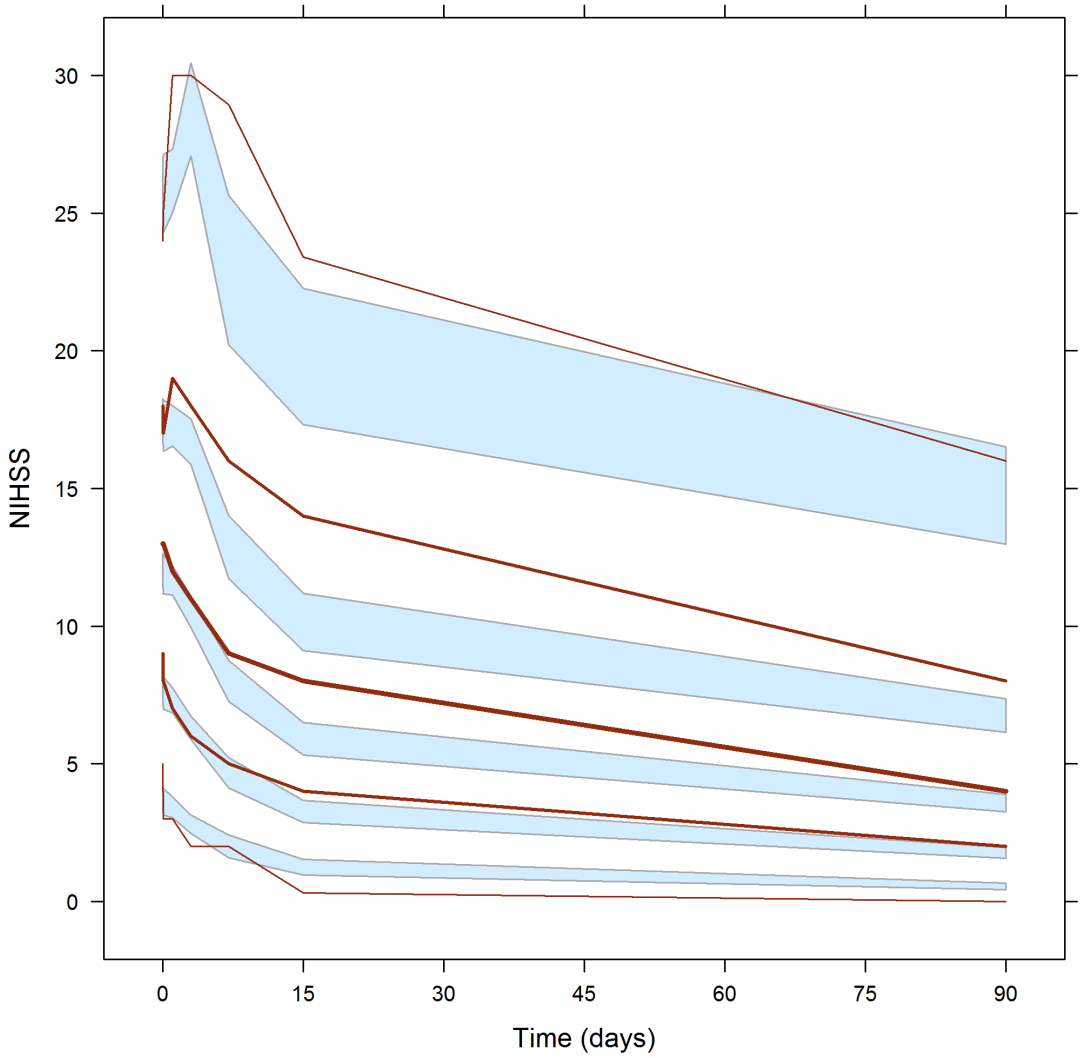


VPCs for mRS capture the observed scores nicely

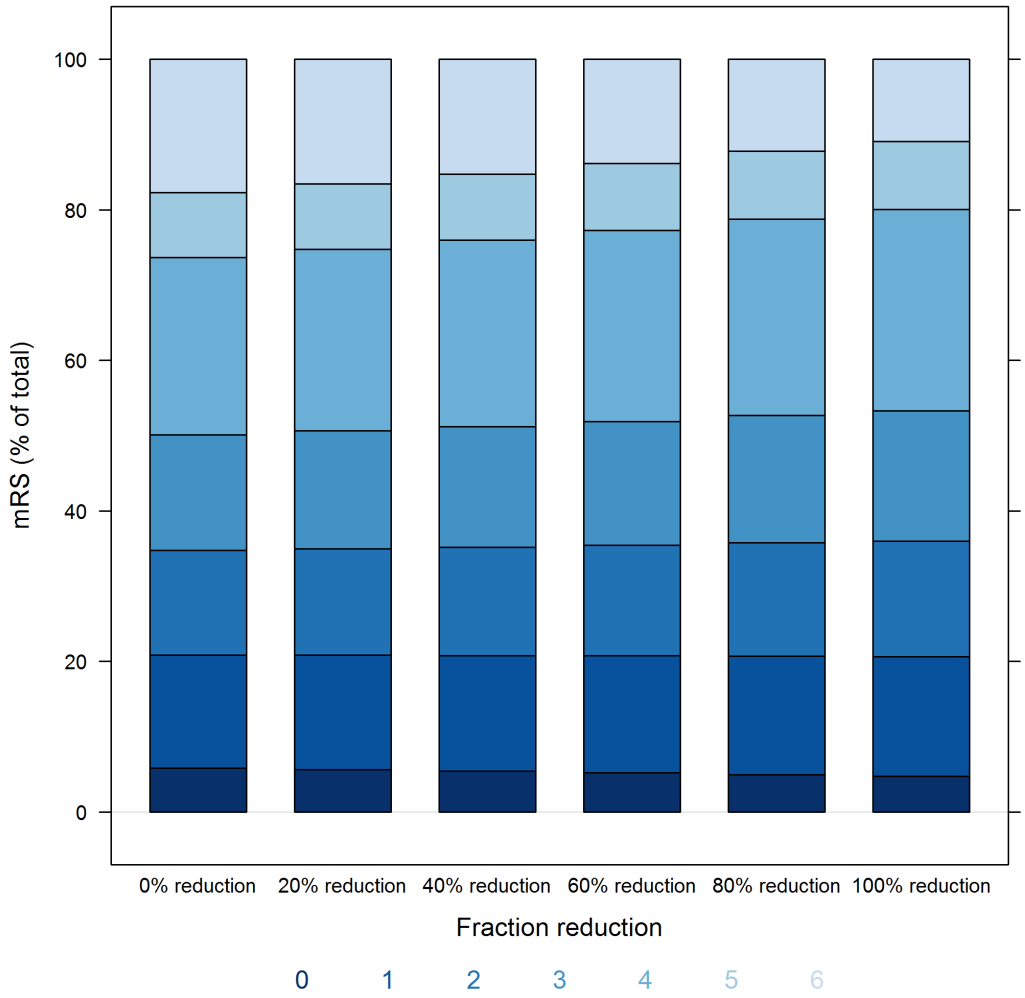


VPCs for NIHSS not perfect yet, but OK at 0 and 90 days

Work in progress



Use the model to simulate the effect of reducing the hematoma volume increase by a certain percentage



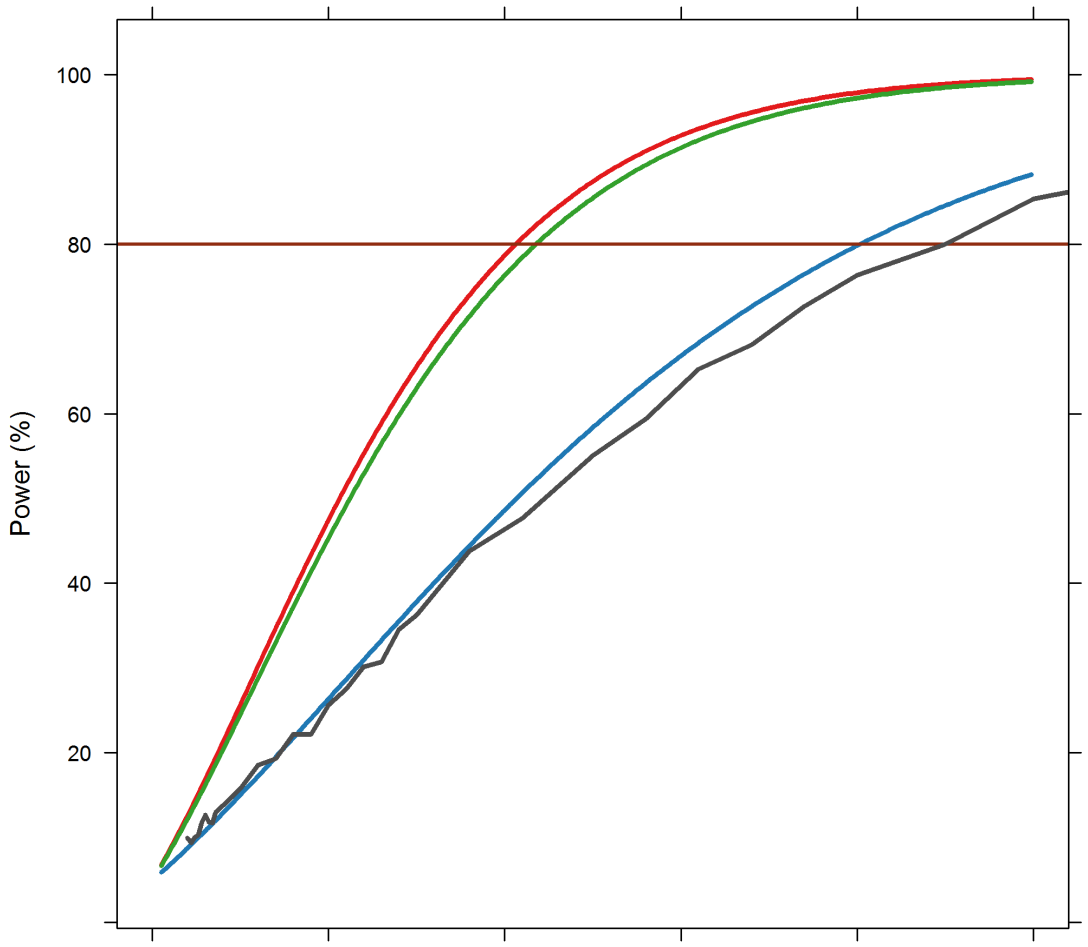
Reduction in volume increase is predicted to reduce the number of deaths

Simulations using Parametric Power Estimation*

- Hypothetical power *vs.* sample size curves generated using PPE
  - visualizing a potential (but fictional) drug effect through the model
  - exemplified here only as 20% increase in E_{max} for improvers and 20% decrease in fraction deterioraters
- Patients were simulated using the current best combined model for mRS and NIHSS
  - Appropriate linkage between endpoints still under discussion
- Simulations analysed with:
  - mRS data at day 90 using standard logistic regression
  - mRS only longitudinal model
  - NIHSS only longitudinal model
  - Combined mRS/NIHSS longitudinal model

*Ueckert S, Karlsson MO, Hooker AC. Accelerating Monte-Carlo Power Studies through Parametric Power Estimation. PAGE 23 (2014) Abstr 3263 [www.page-meeting.org/?abstract=3263]

Preliminary assessment on performance characteristics across the different hypothetical endpoints – not for implementation at this stage …



- Combined model mRS/NIHSS
- NIHSS alone
- mRS alone (2-3 measurements)
- Logistic regression on mRS at D90

Conclusions

- The combined model allows simultaneous description of mRS and NIHSS
- Reductions in hematoma volume increase may have to be substantial before they impact mRS scores
- mRS and NIHSS appear to behave comparably
- Adding/use of NIHSS data may lead to an increase in the sensitivity to identify a treatment effect
- **Future model updates:**
  - will attempt to more accurately describe the NIHSS profile, incorporating a dropout due to death component
  - will explore alternatives to the proposed composite endpoint
  - will explore alternatives to hypothesize a treatment effect

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