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Modeling disease progression in acute stroke by simultaneously using the NIH Stroke Scale, Scandinavian Stroke Scale and the Barthel Index

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Acute ischemic stroke

- 12 million people suffer acute ischemic strokes each year[1]
  - One third die
  - One third are left permanently disabled

[1]Atlas of Heart Disease and Stroke, WHO, September 2004

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Clinical trials in acute ischemic stroke

- More than 74 000 patients with acute ischemic stroke have been randomized into clinical trials over the past 35 years[1]

- Only one treatment has emerged from these investigations! (tPA treatment)

[1]Krams M, Lees KR, Berry DA. The past is the future: Innovative Designs in Acute Stroke Therapy Trials. *Stroke* 2005;36;1341-1347.

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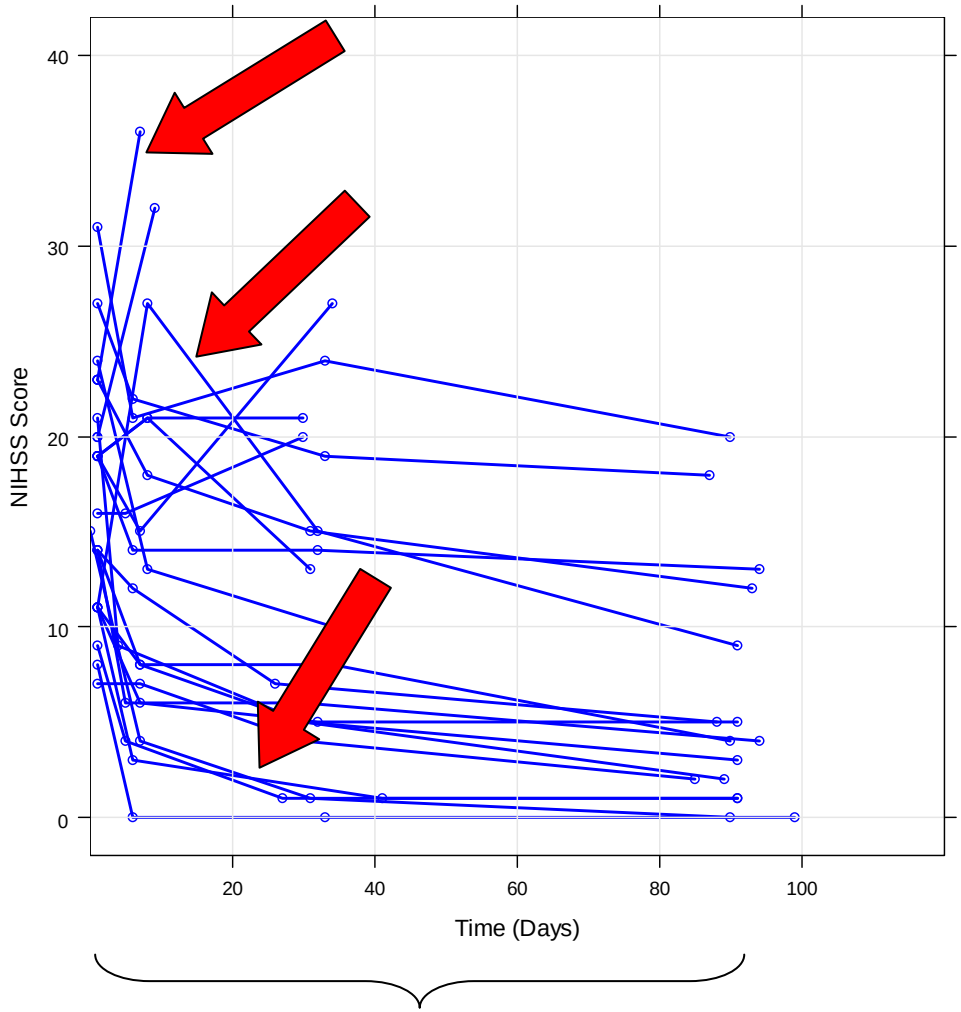
Challenges in drug development

- The nature of stroke is challenging
  - Multi-factorial disease
- Lack of informative biomarkers
- Several scales used
  - Neurological assessment
  - Functional assessment
- Blunt endpoints
  - Disease progression
  - The scales as such

Example of stroke data – measured on the NIH stroke scale



Dropout pattern

Non-monotonic pattern

Monotonic improvement pattern

Approved clinical end-point = Day 90-Day0

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What would the benefits of modeling be in establishing clinical efficacy in stroke?

- Longitudinal analysis would use all the available information within one subject
- Appropriate handling of dropouts
- With modeling is it possible to look across scales and utilize the available information optimally

→ Easier to establish a drug effect

→ Will increase the statistical power

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Objectives

- To develop a single disease progression model for multiple stroke scales
  - That can be fitted to multiple scales simultaneously
  - That uses all assessments on all scales, including dropout

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Data used in the development of the disease progression model

- Placebo arm from an efficacy trial of Chlomethiazole
- 772 patients
- *NIH Stroke Scale* – Neurological assessment
  - Scores between 42 – 0
  - Day 0, 7, 30, and 90
- *Scandinavian Stroke Scale* – Neurological assessment
  - Scores between 0 – 48
  - Day 0, 7, 30, and 90
- *Barthel Index* – Functional assessment
  - Scores between 0 – 100 (increments of 5)
  - Day 7, 30, 60, and 90

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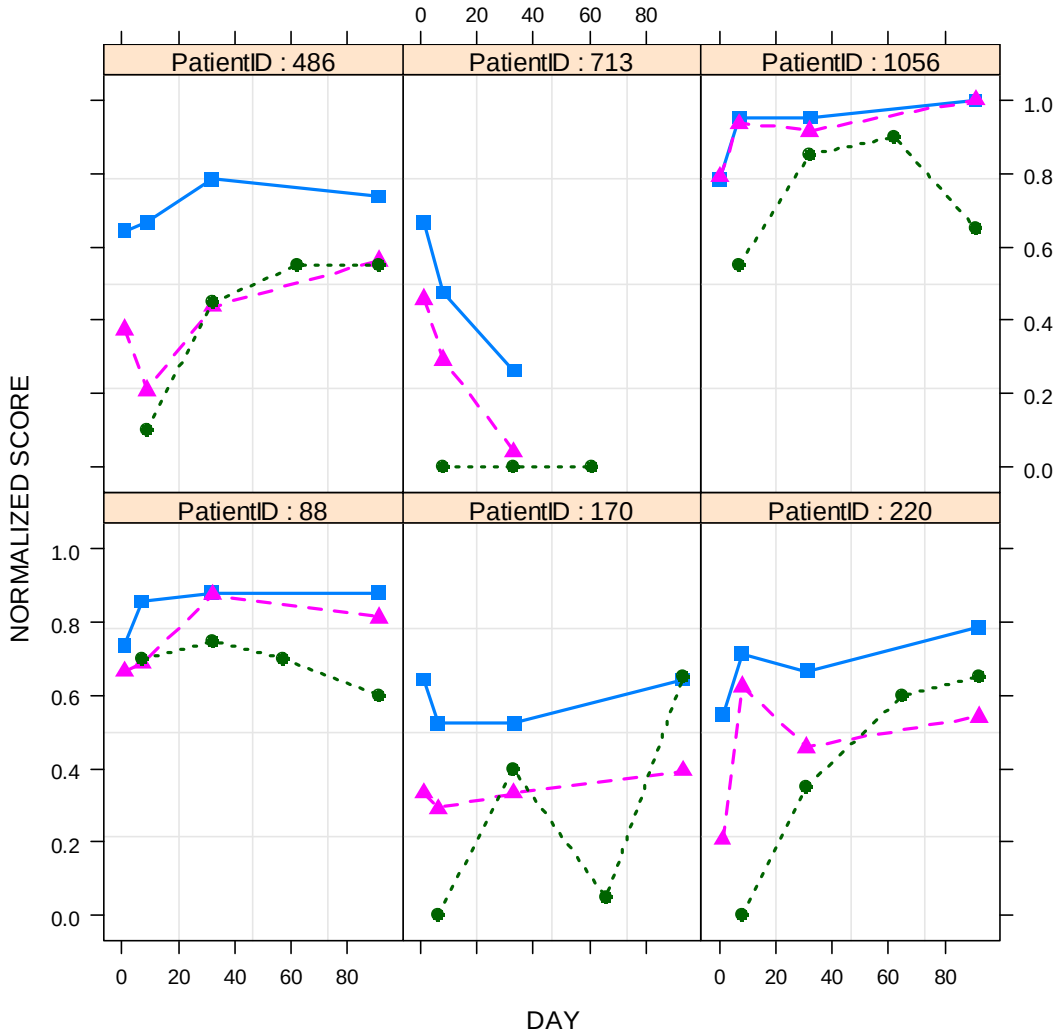
Individual stroke scores measured on three different stroke scales



- Normalized scores: between 0-1
- 1 is good , 0 is bad

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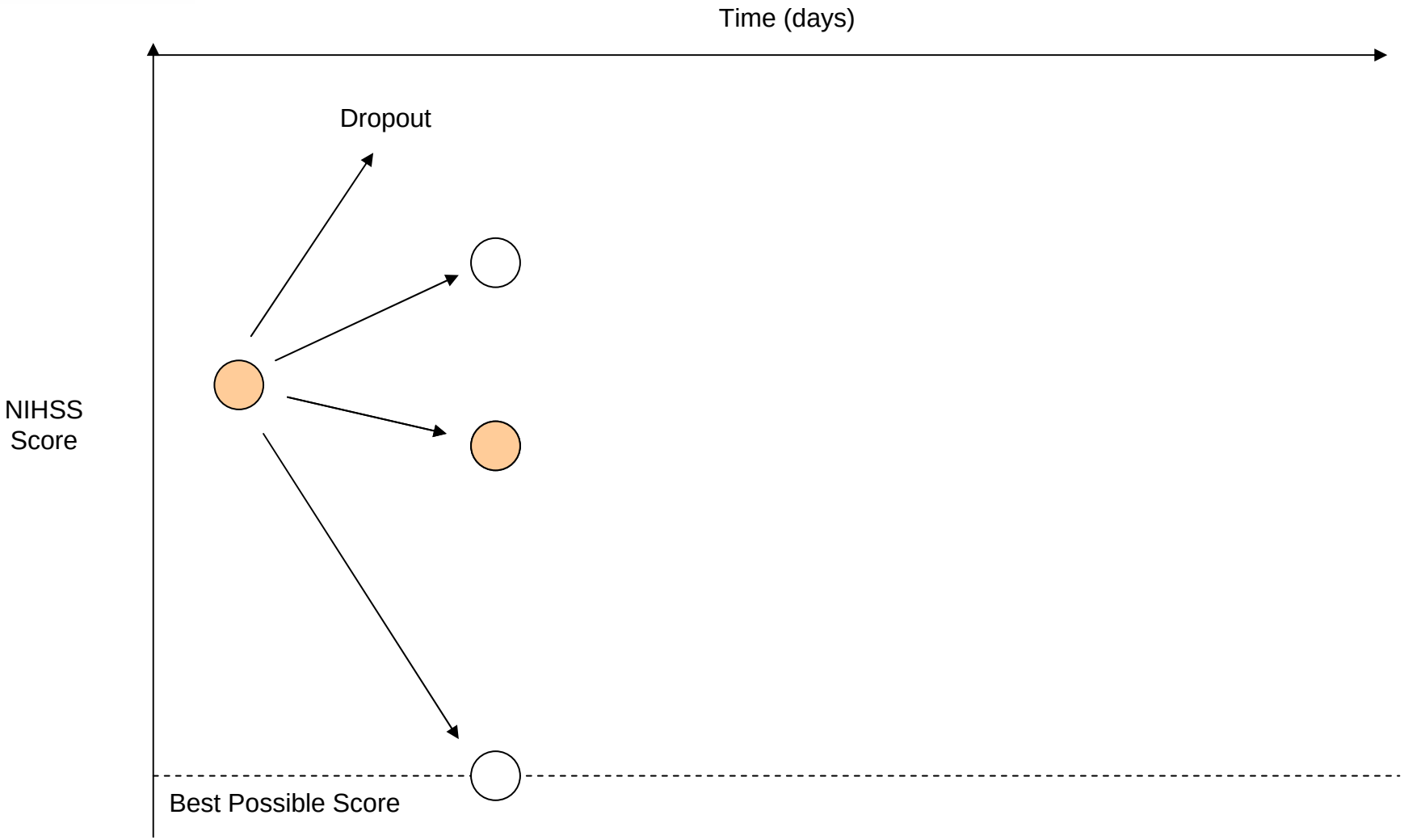
A longitudinal model for a *scale specific disease progression* in acute stroke



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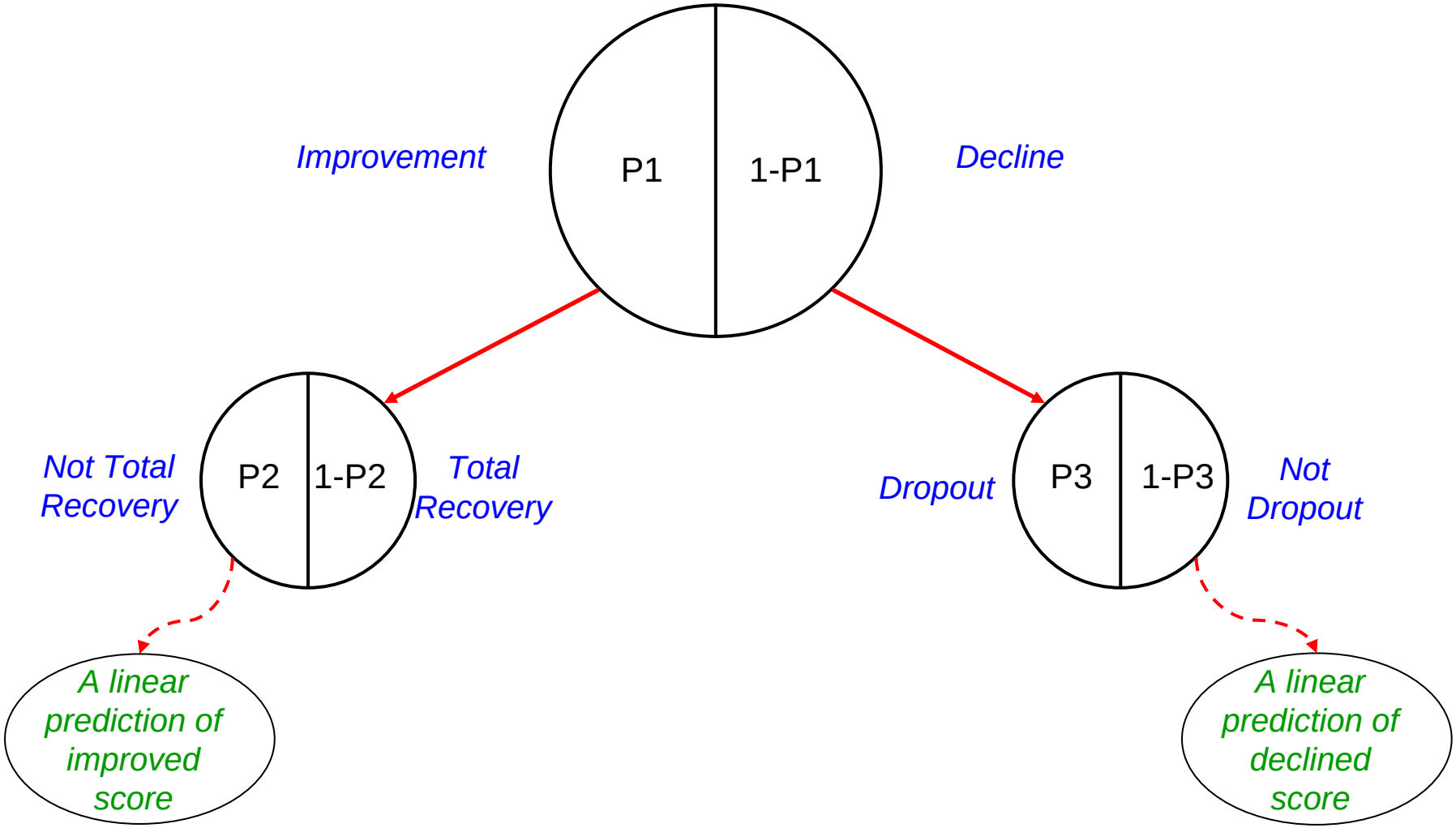
Schematic picture of the hierarchy of the *scale specific model*



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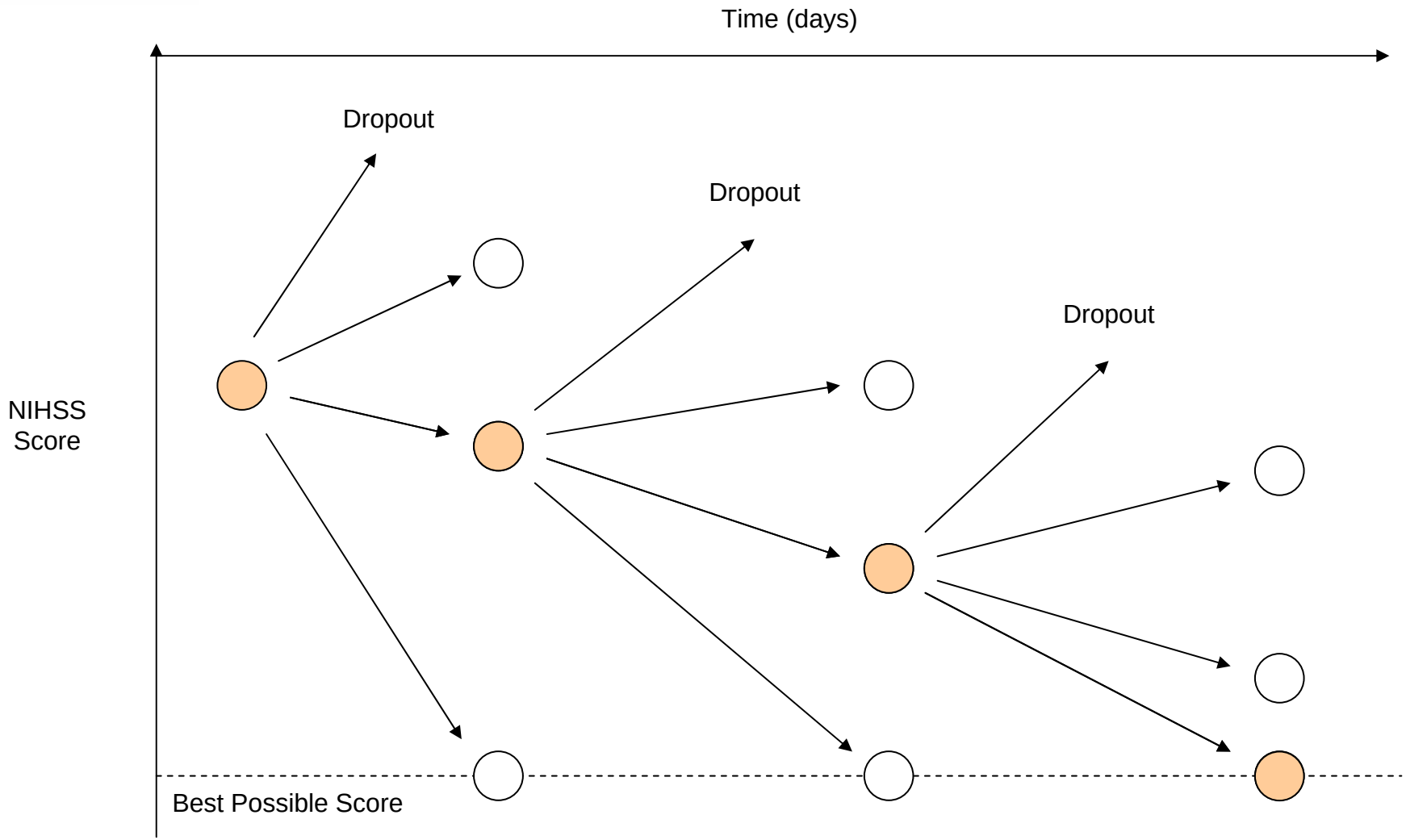
A longitudinal model for a *scale specific disease progression* in acute stroke



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The structure of the *multi-scale model*

Scale specific components of the model:

- ✓Probability of improvement
- ✓Probability of not total recovery
- ✓Relative score improvement + IIV
- ✓Relative score decline + IIV

Scale independent components of the model:

- ✓IIV covariance on relative score improvement
- ✓IIV covariance on relative score decline
- ✓Dropout model

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Structural covariates included in the multi-scale model

	NIHSS	***SSS***	***BI***	***Joint***
Probability of Improvement				
Y_{j-1}			•	
Age		•	•	
Probability of Not Total Recovery				
Y_{j-1}	•	•	•	
$\Delta(t_j-t_{j-1})$			•	
Probability of Dropout				
$\hat{Y}_{SSS}$				•
$\Delta(t_j-t_{j-1})$				•
Relative Score Improvement				
Y_{j-1}			•	
Age			•	
Relative Score Decline				
Y_{j-1}	•	•	•	
$\Delta(t_j-t_{j-1})$	•	•	•	

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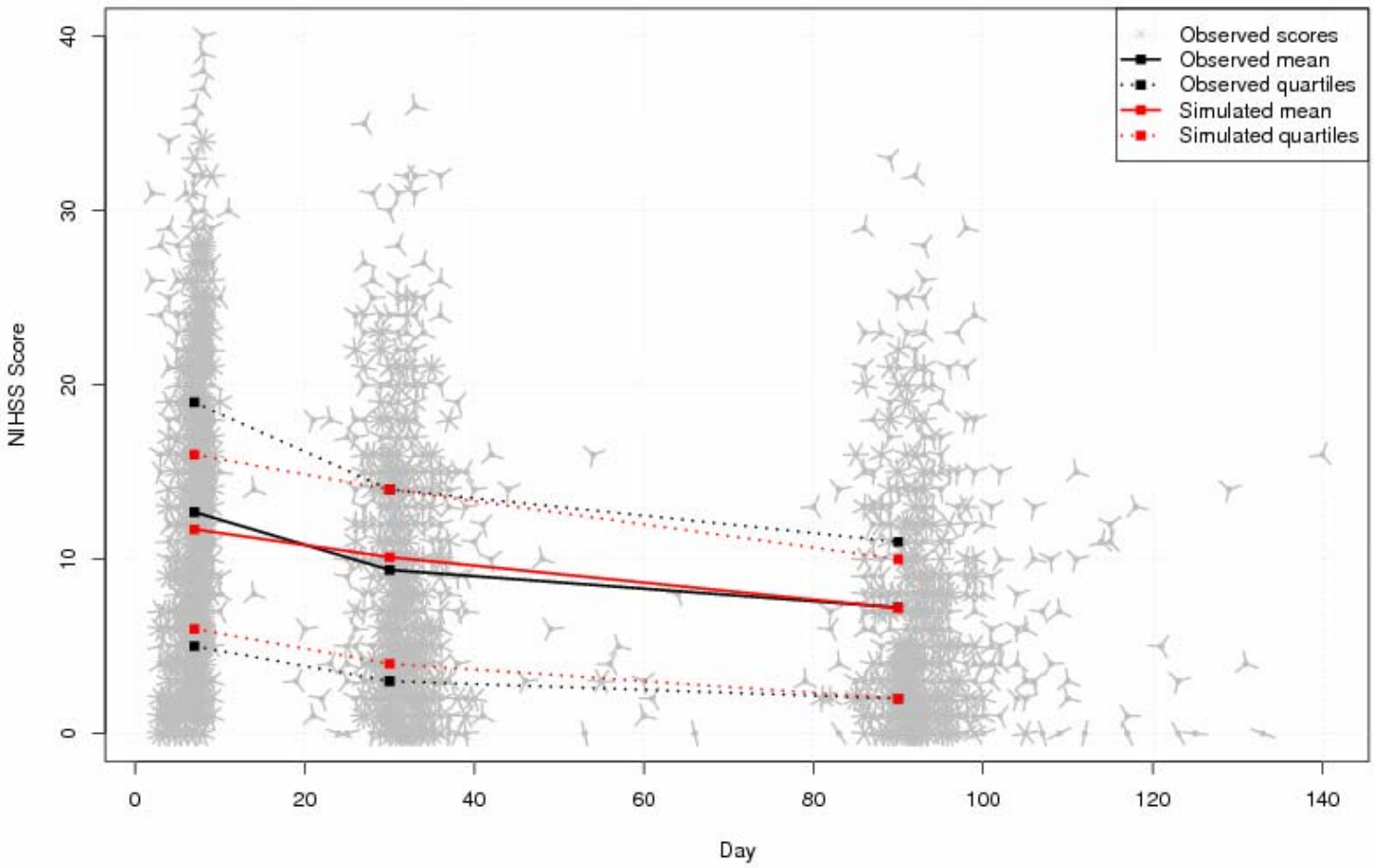
Results – NIH stroke scale



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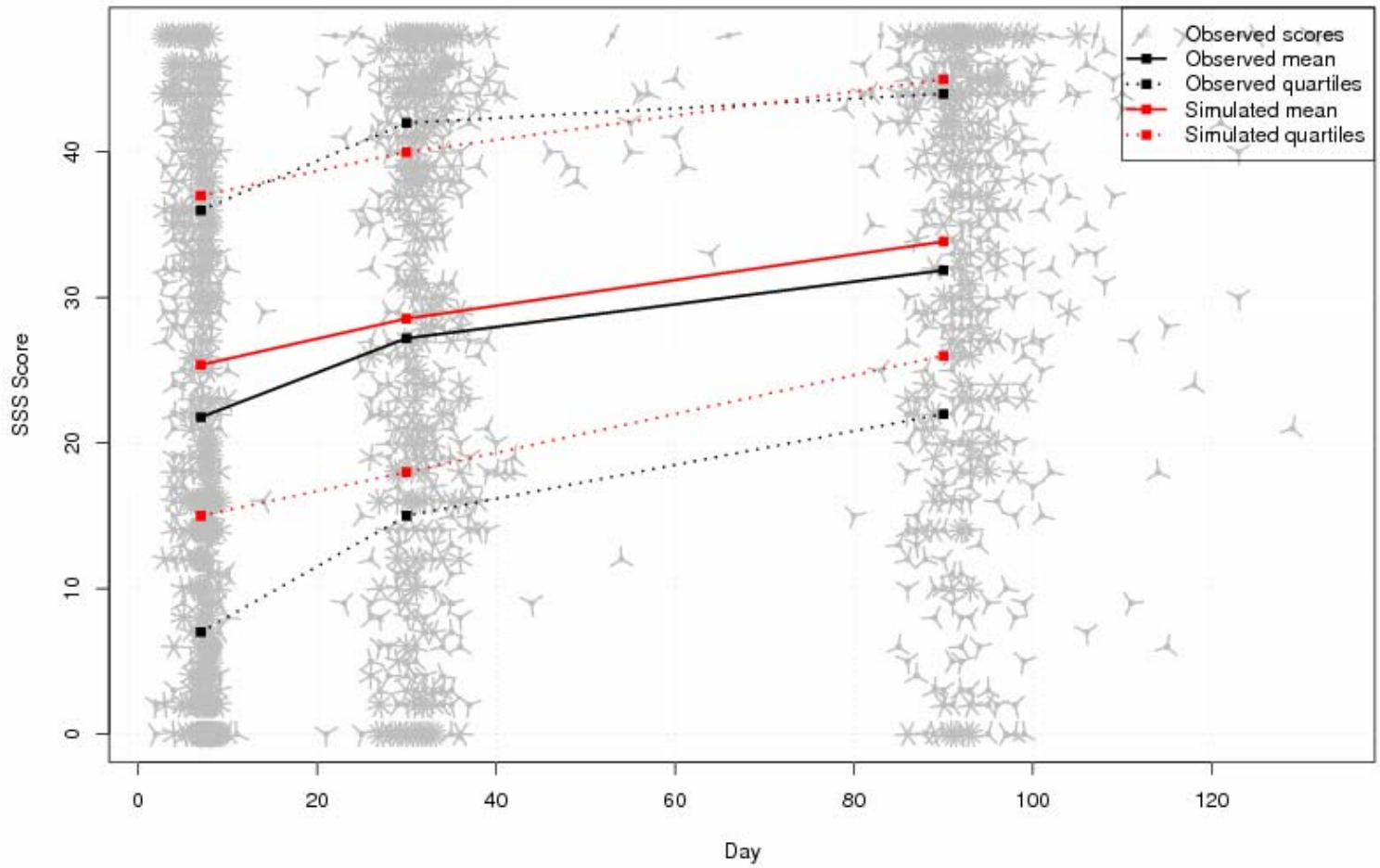
Results – Scandinavian stroke scale



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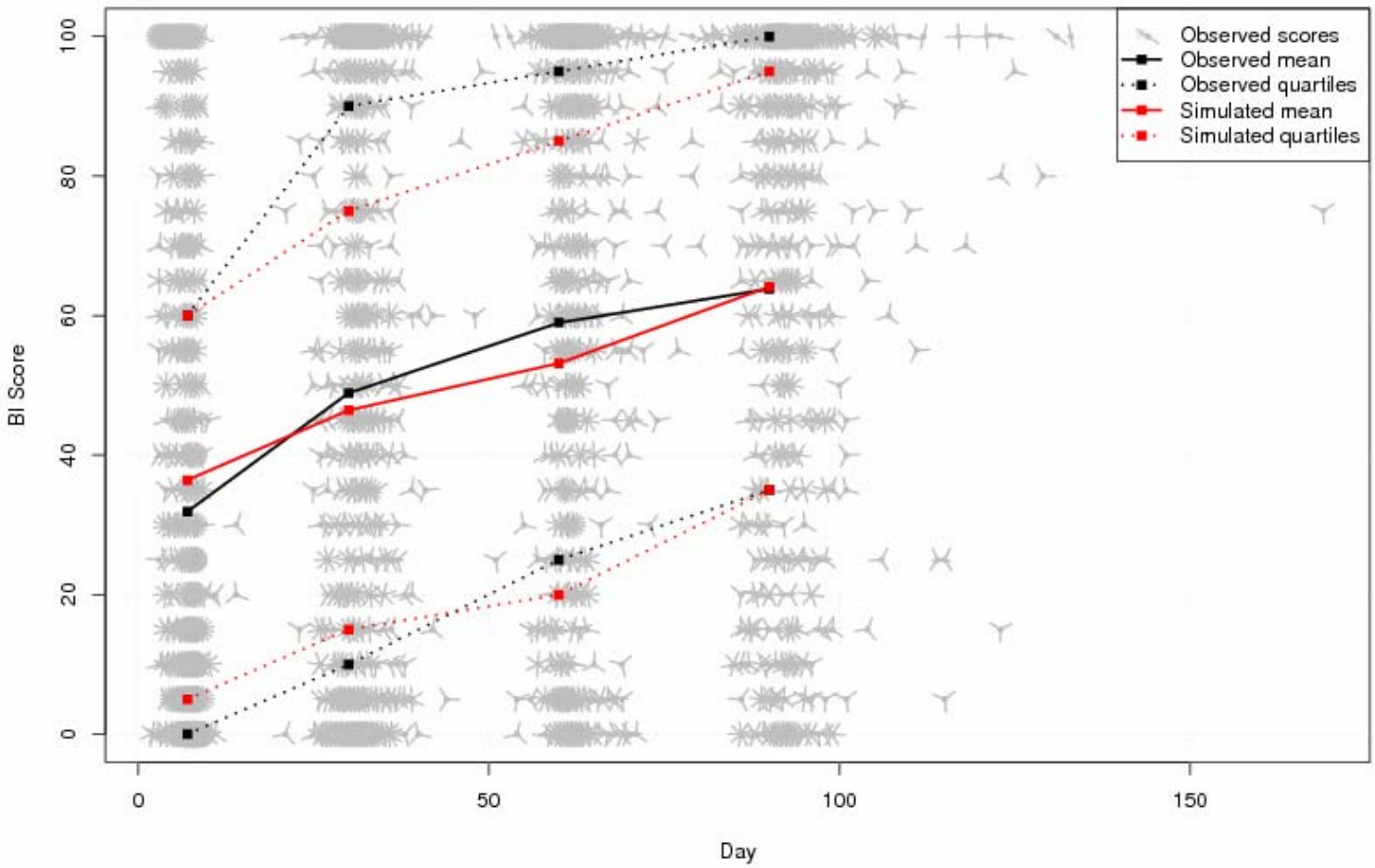
Results – Barthel Index



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Summary

- A model that recognizes similarities and accounts for differences for measurements on multiple stroke scales has been developed. It incorporates:
  - ✓ Disease progression
  - ✓ Structural covariates
  - ✓ A common dropout model
  - ✓ Covariance between interindividual variabilities across the three scales

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