Rescue Behavior and Imputation Strategies in Analgesic Studies

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Indication for Pain

- Pain indications
  - General pain
    - Acute Pain
    - Chronic Pain
  - Pain due to specific cause
    - Osteoarthritis
    - Diabetic Neuropathy

Acute Pain

- Duration of Pain up to 3 months
  - Post-operative Pain
    - Dental Surgery
    - Bunionectomy
    - Joint Replacement Surgery
  - Pain due to injury that is not chronic
    - Joint Dislocation
    - Emergency room visit

Chronic Pain

- Duration of Pain longer than 3 months
  - Pain due to chronic condition
    - Osteoarthritis (OA)
    - Rheumatoid Arthritis (RA)
    - Low Back Pain (LBP)
    - Diabetic Neuropathy
    - Cancer
  - Treatment pain does not necessarily treat the underlying disease condition

Clinical Trials in Acute Pain

- Short Duration
  - Single-dose
  - Multiple-doses for 1-3 days
  - Frequent assessments for pain intensity and pain relief within a day
  - For post-operative pain:
    - Immediately after surgery
    - One day after surgery

Clinical Trials in Chronic Pain

- Long Duration
  - Minimum 12-weeks
  - Often 12-weeks exclude titration period
  - Fixed-dose vs. flexible dose
  - Daily assessments for pain intensity and pain relief (1-2 times a day)
  - Visits scheduled weekly, bi-weekly, monthly

Endpoints in Pain Studies

- Acute Pain
  - Sum of pain intensity and/or pain relief during the treatment period (longitudinal data)
  - Time to perceptible/meaningful pain relief
- Chronic Pain
  - Average weekly pain intensity
  - Pain intensity at last visit
  - AUC of pain intensity over the treatment period

Issues in Pain Studies

- Use of rescue medication
  - Reduces discontinuation due to lack of efficacy
  - More placebo subjects may use rescue and confound the results
- Non-Compliance
- Discontinuation
- Placebo effect

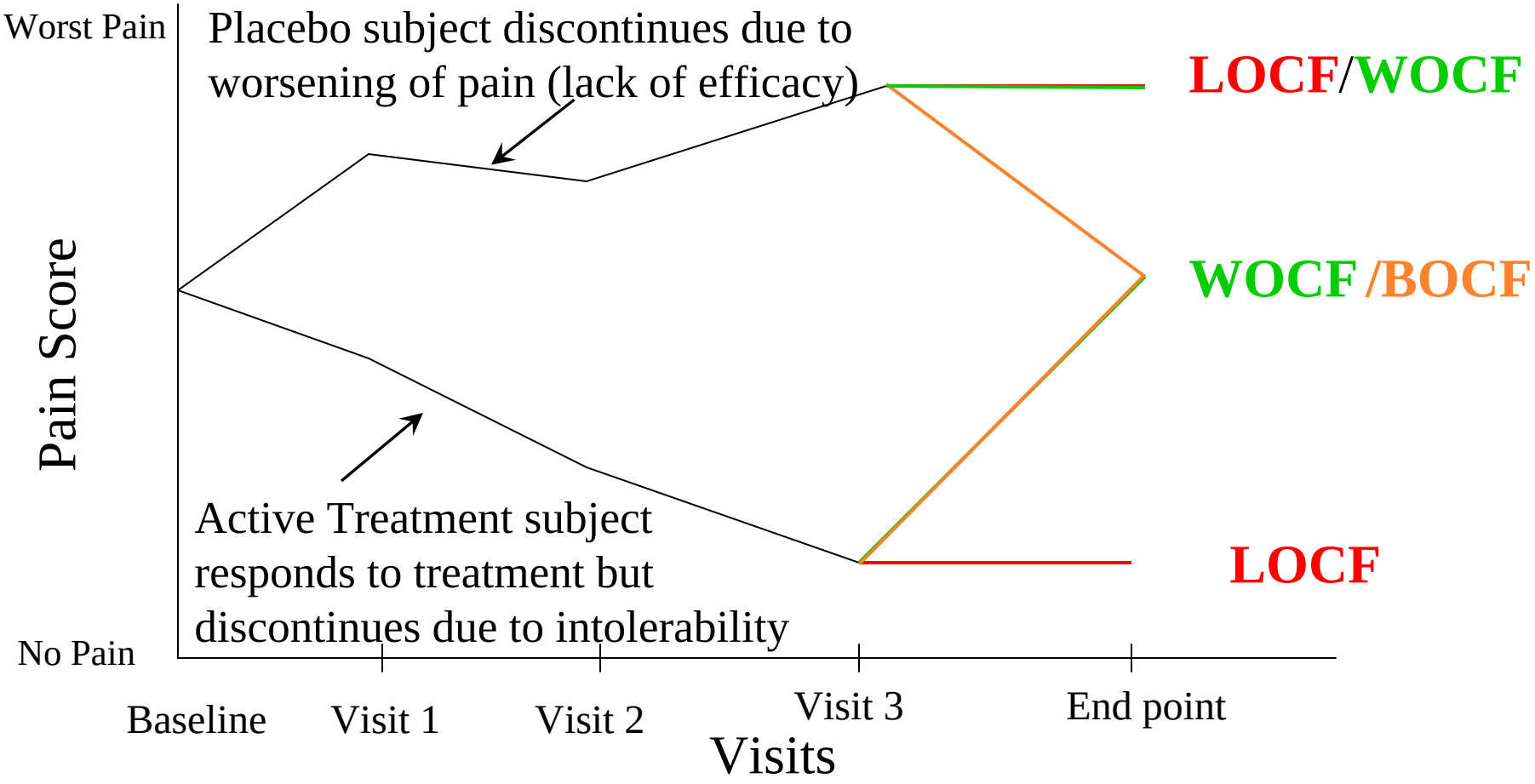
Points for Consideration

- No formal FDA pain guidelines available
- Evolving recommendations on study designs and statistical methods from FDA
  - Moving from fixed dose designs to more flexible dosing
  - Rescue Medication Strategies
  - Choice of imputation method for subjects who discontinue early from the trial and implications on the analysis

Data Imputation

- Missing data arise when a subject misses visits or discontinues from the study for any reason
- Data imputation is a strategy to deal with the missing data in the analyses
- No Imputation method is perfect
- Possible choices:
  - Last Observation Carried Forward (LOCF)
  - Baseline Observation Carried Forward (BOCF)
  - Worst Observation Carried Forward (WOCF)
  - Group Mean Imputation (GMI)
  - Placebo Mean Imputation (PMI)
  - Imputation based on Reason for discontinuation (IDUR)
  - Other

LOCF, BOCF, WOCF Illustrations



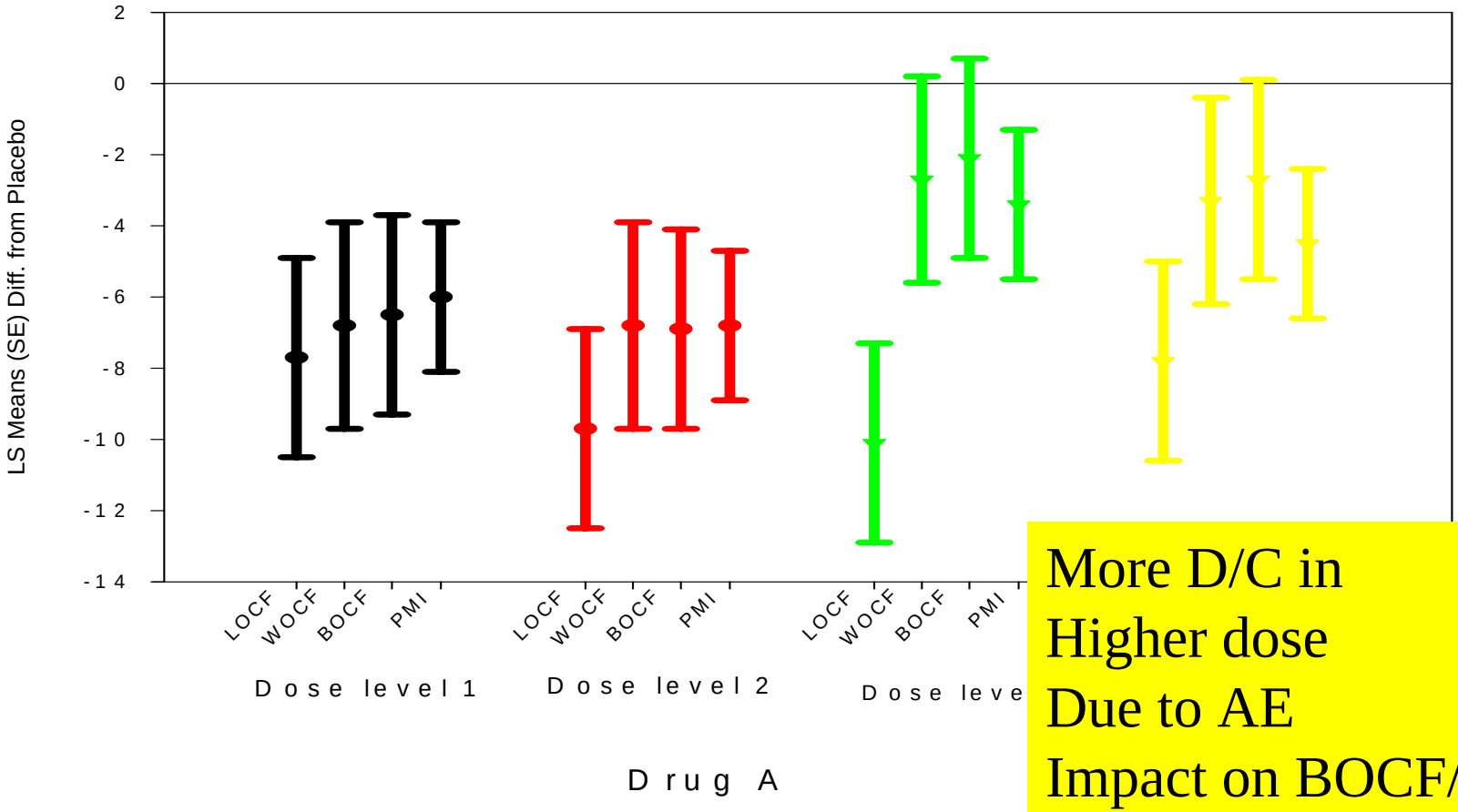
FDA's View on Imputation Methods

- LOCF is no longer acceptable
  - The last observation is often the best observed for subjects who discontinued due to intolerability
  - Carrying forward the best possible result will bias in favor of the active treatment
- BOCF, WOCF or other conservative approach is preferred (e.g. impute with mean of the placebo group)

Impact on change in imputation methods

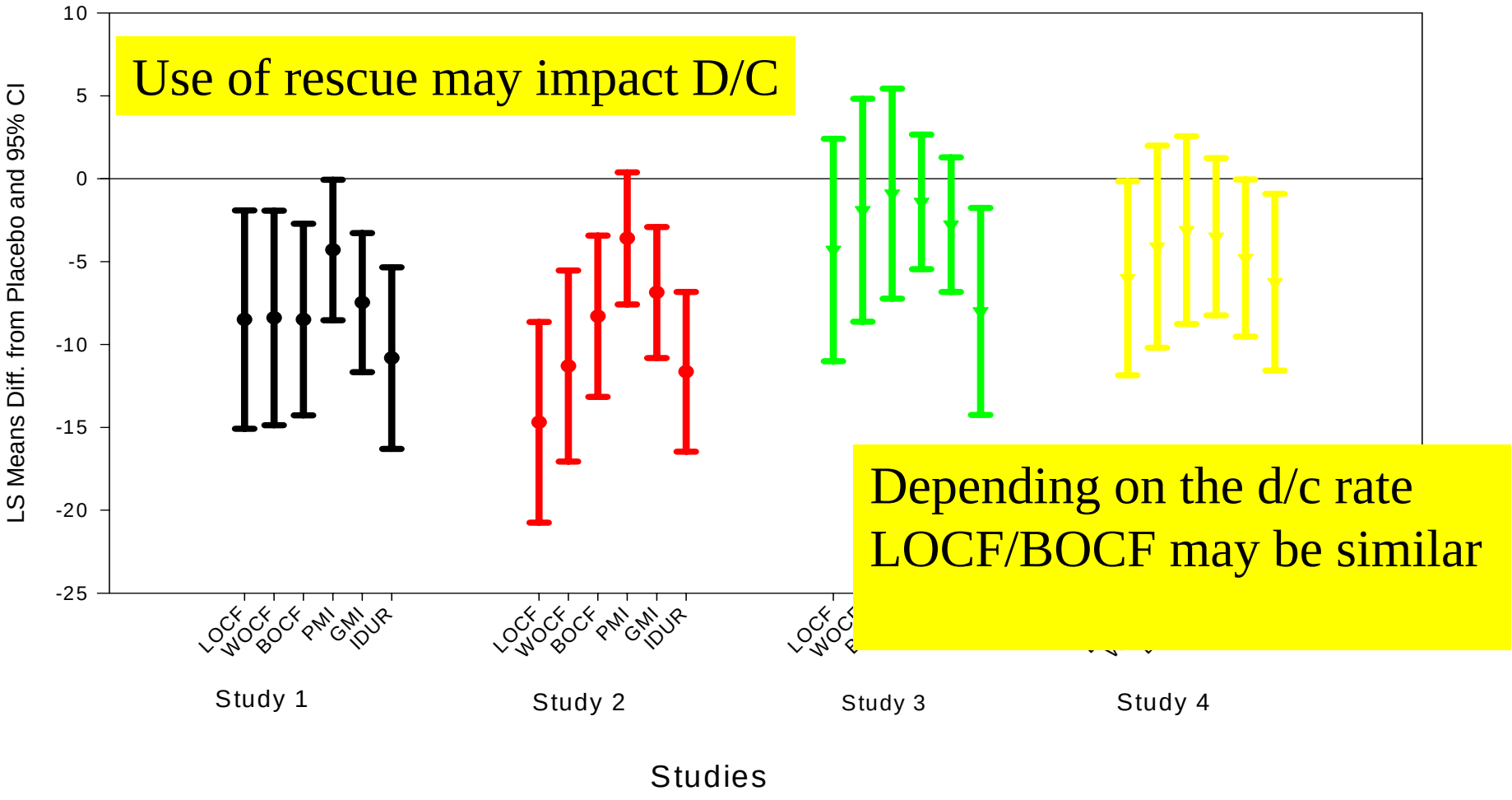
- Effect sizes will vary based on choice of imputation methods
  - Impact on sample sizes
- Impact on clinically meaningful difference?

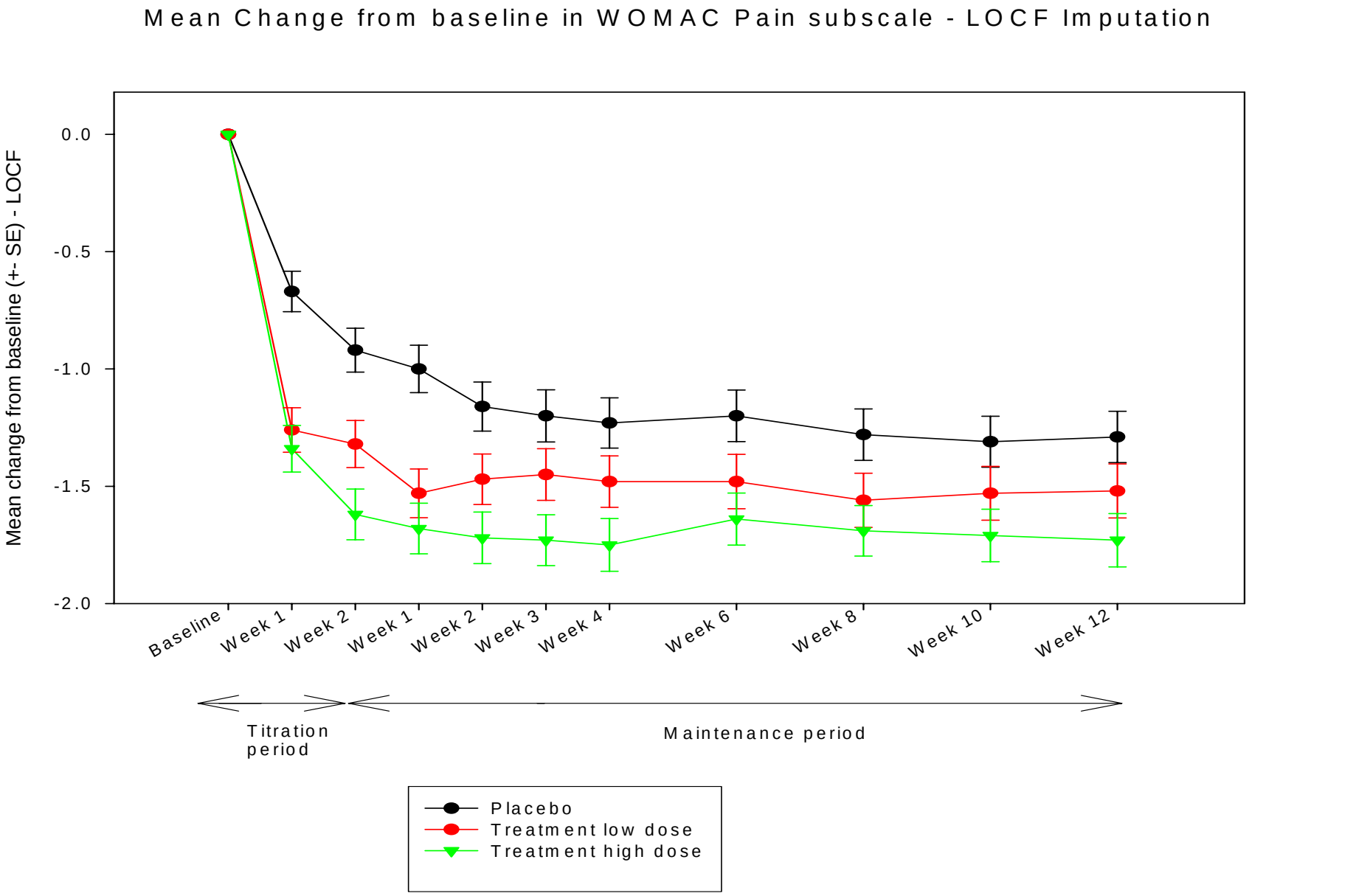
Previous Fixed Dose Pain Studies: LS Means Difference from Placebo and 95% CI



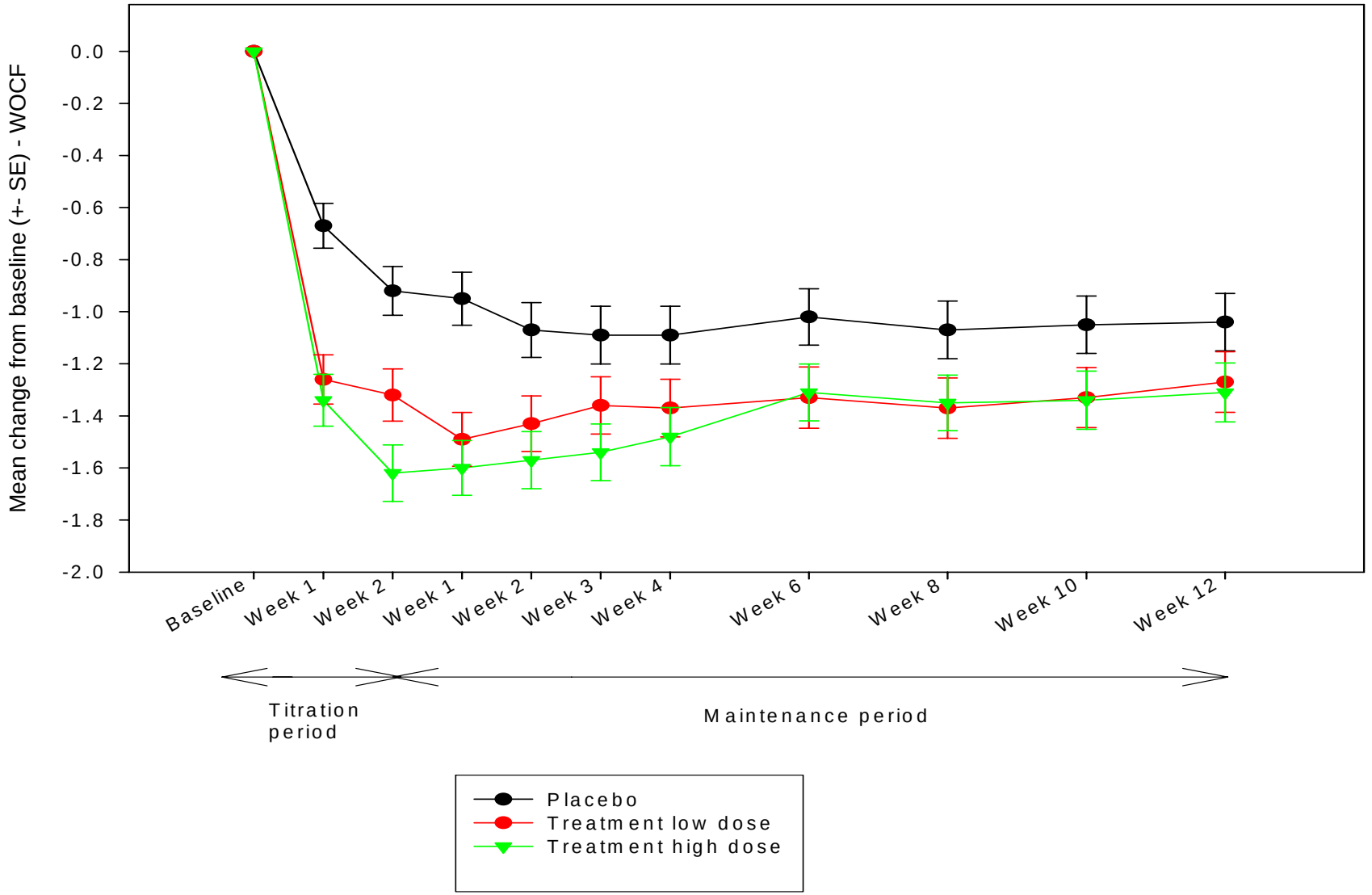
More D/C in
Higher dose
Due to AE
Impact on BOCF/WOCF

Previous Flexible Dose Pain Studies: LS Means Difference from Placebo and 95% CI

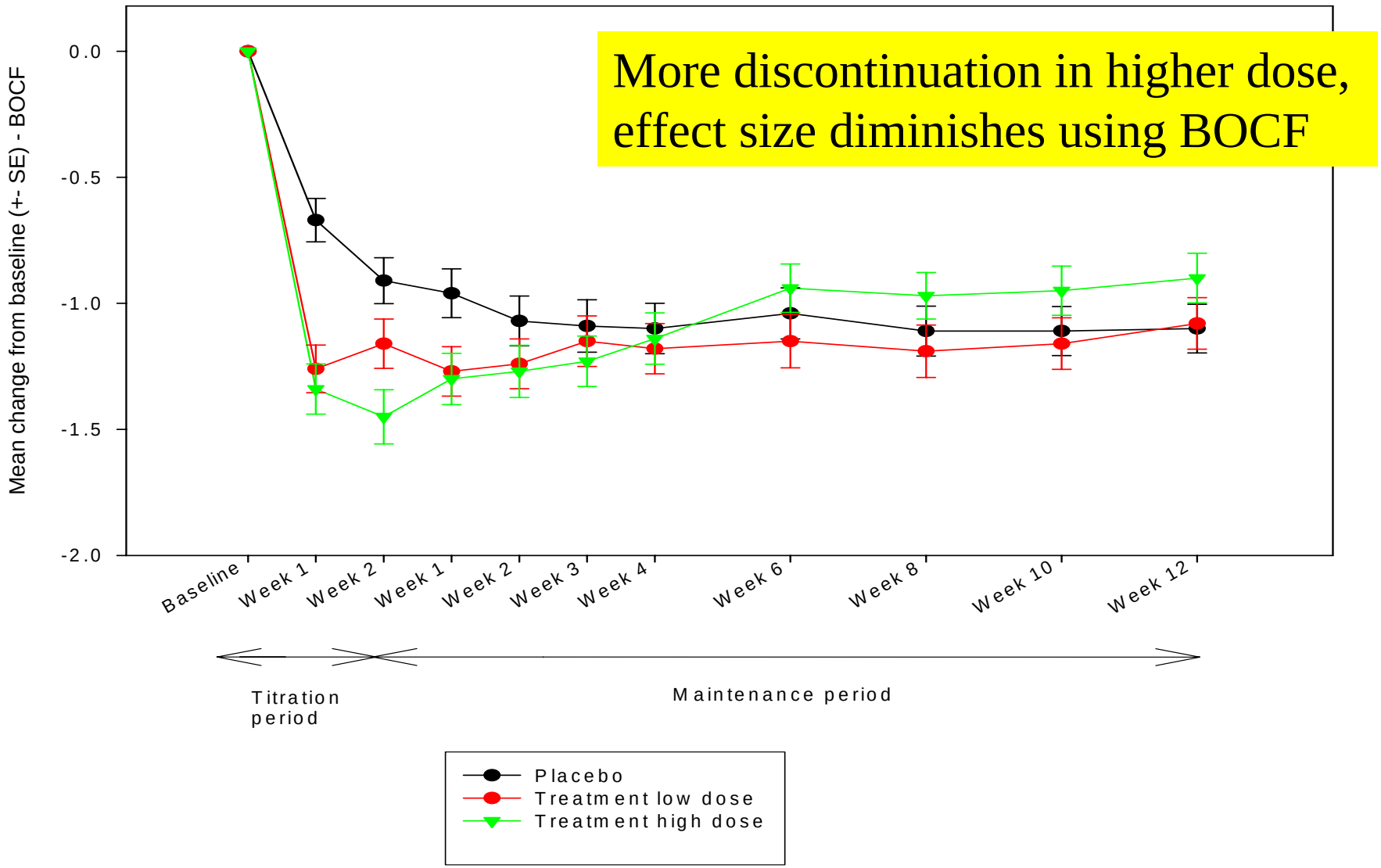



Mean Change from baseline in WOMAC Pain subscale - LOCF Imputation
Mean change from baseline (+- SE) - LOCF
0.0
-0.5
-1.0
-1.5
-2.0
Baseline
Week 1
Week 2
Week 1
Week 2
Week 3
Week 4
Week 6
Week 8
Week 10
Week 12
Titration period
Maintenance period
Placebo
Treatment low dose
Treatment high dose

Mean Change from baseline in WOMAC Pain subscale - WOCF Imputation



Mean Change from baseline in WOMAC Pain subscale - BOCF Imputation



Imputation Methods

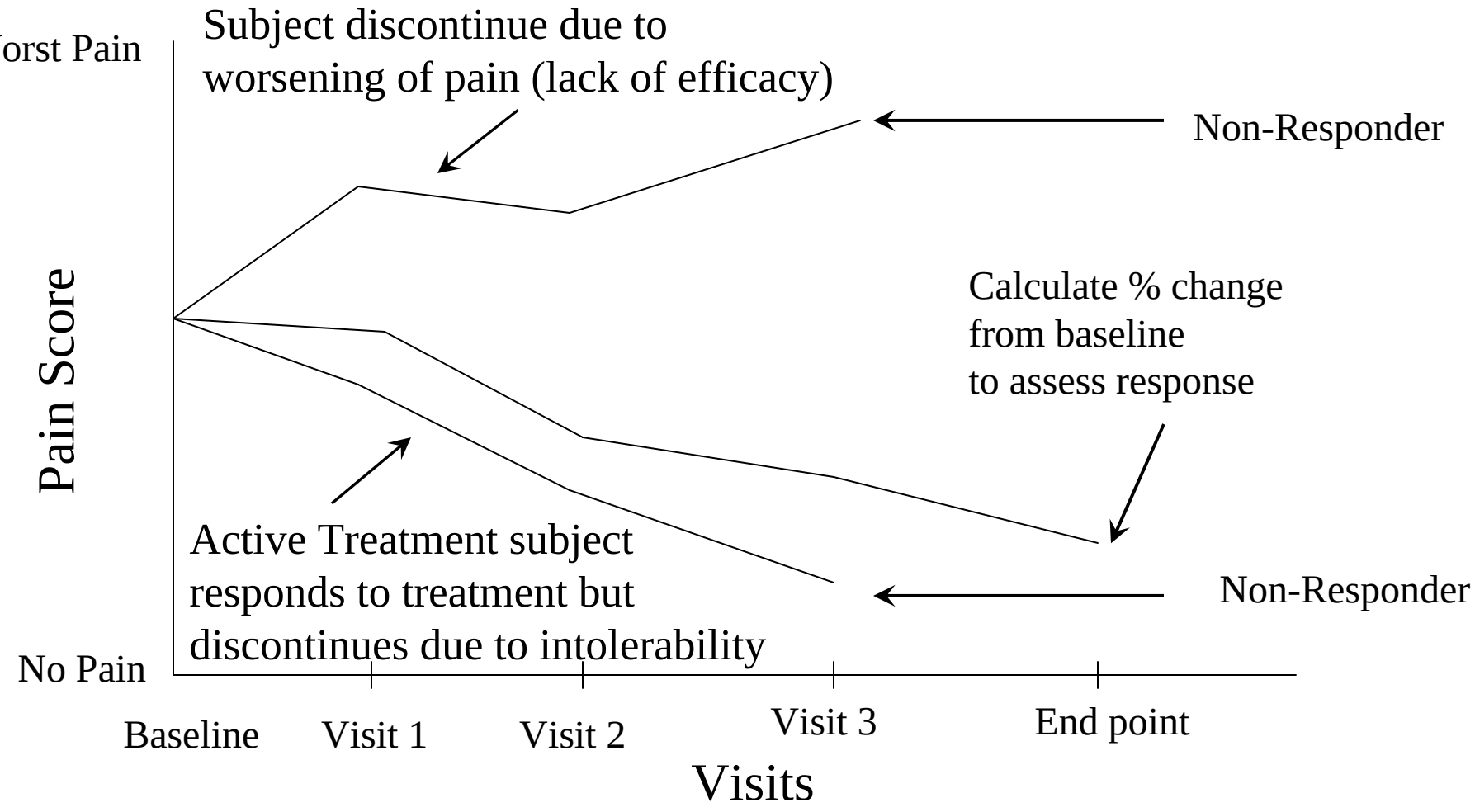
- Choice of imputation may impact the results of the statistical analyses

- Another approach to deal with missing data recommended by FDA – Responder analysis

Responder analysis

- Based on percent change from baseline in pain score at end point.
- Subjects who discontinued are considered to be non-responders regardless of the pain score and reason for discontinuation.

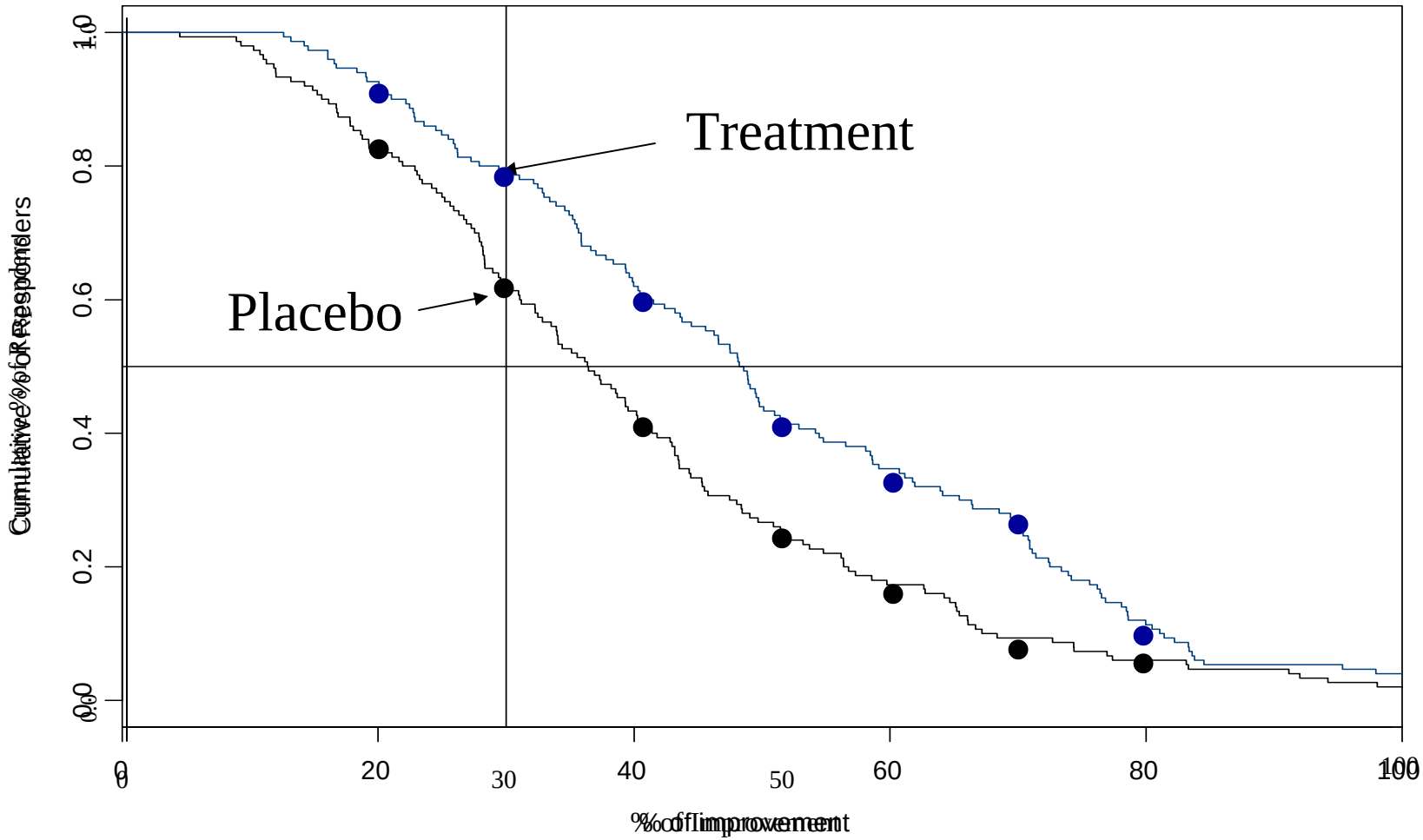
Responder Illustrations



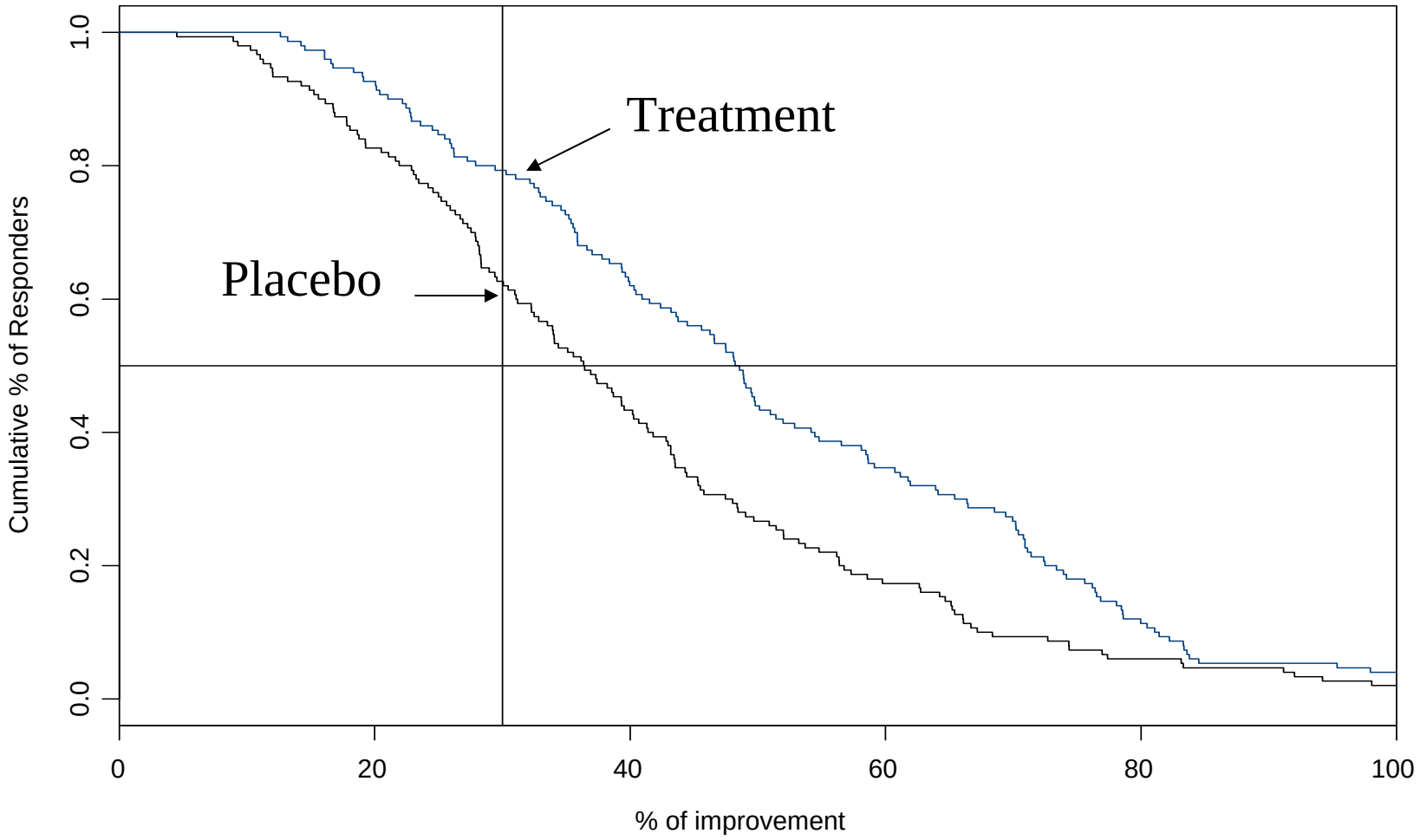
Responder analysis

- There will be a ceiling in the number of responders based on the dropout rate
- Higher the dropout in the treatment group due to AE, more difficult to show treatment difference
- It is similar to BOCF
- It still requires a form of imputation

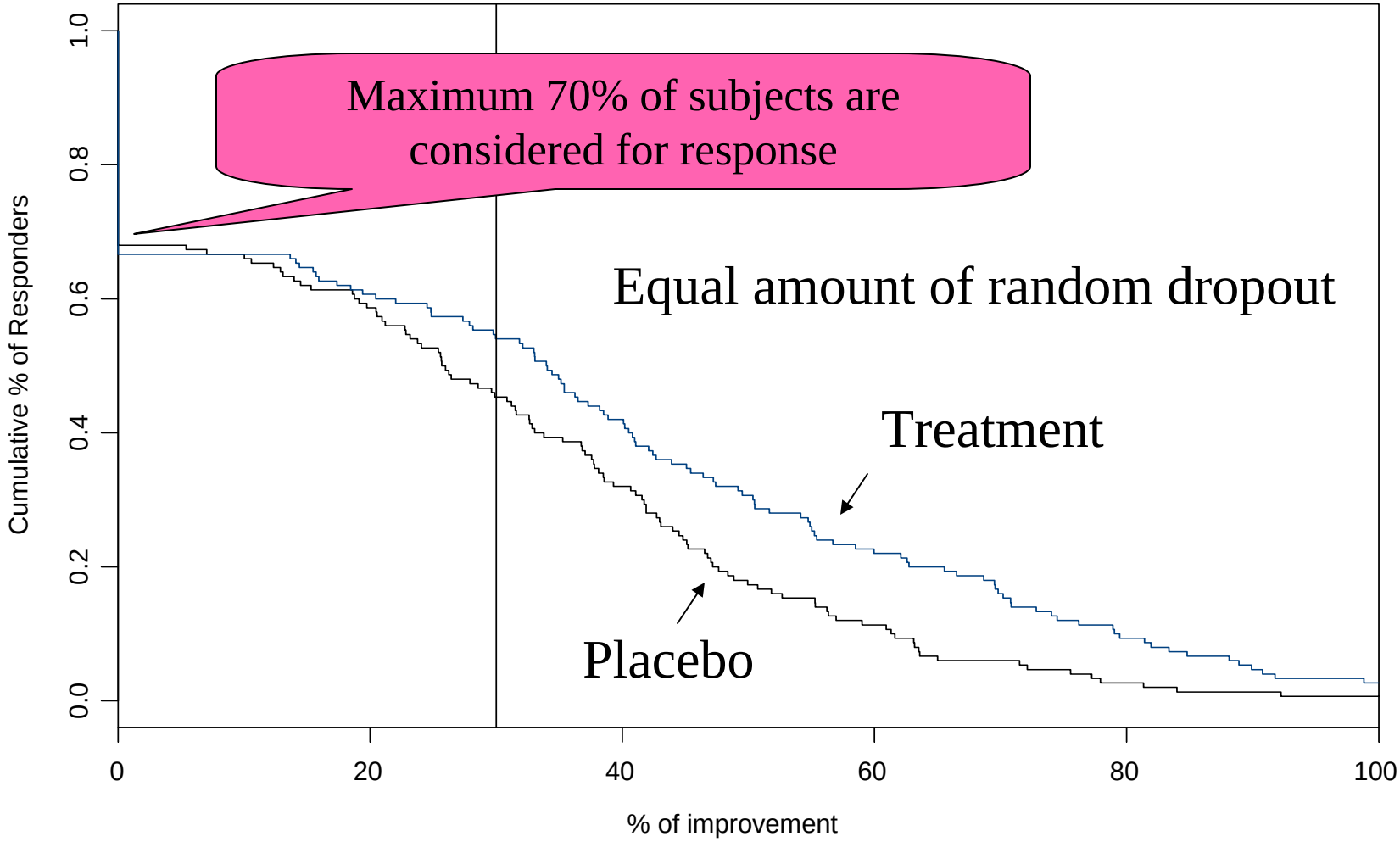
How does it look like?



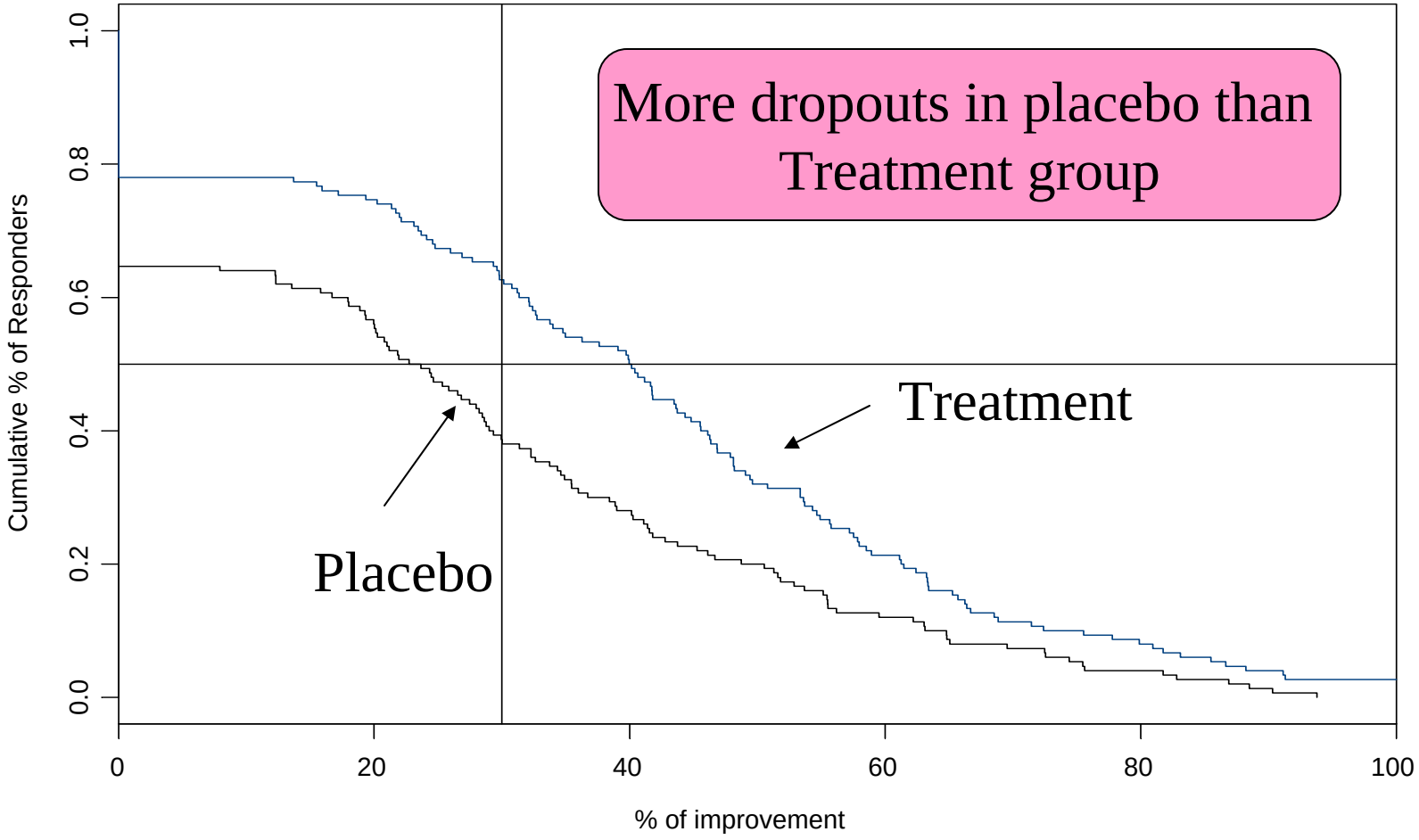
How does it look like?



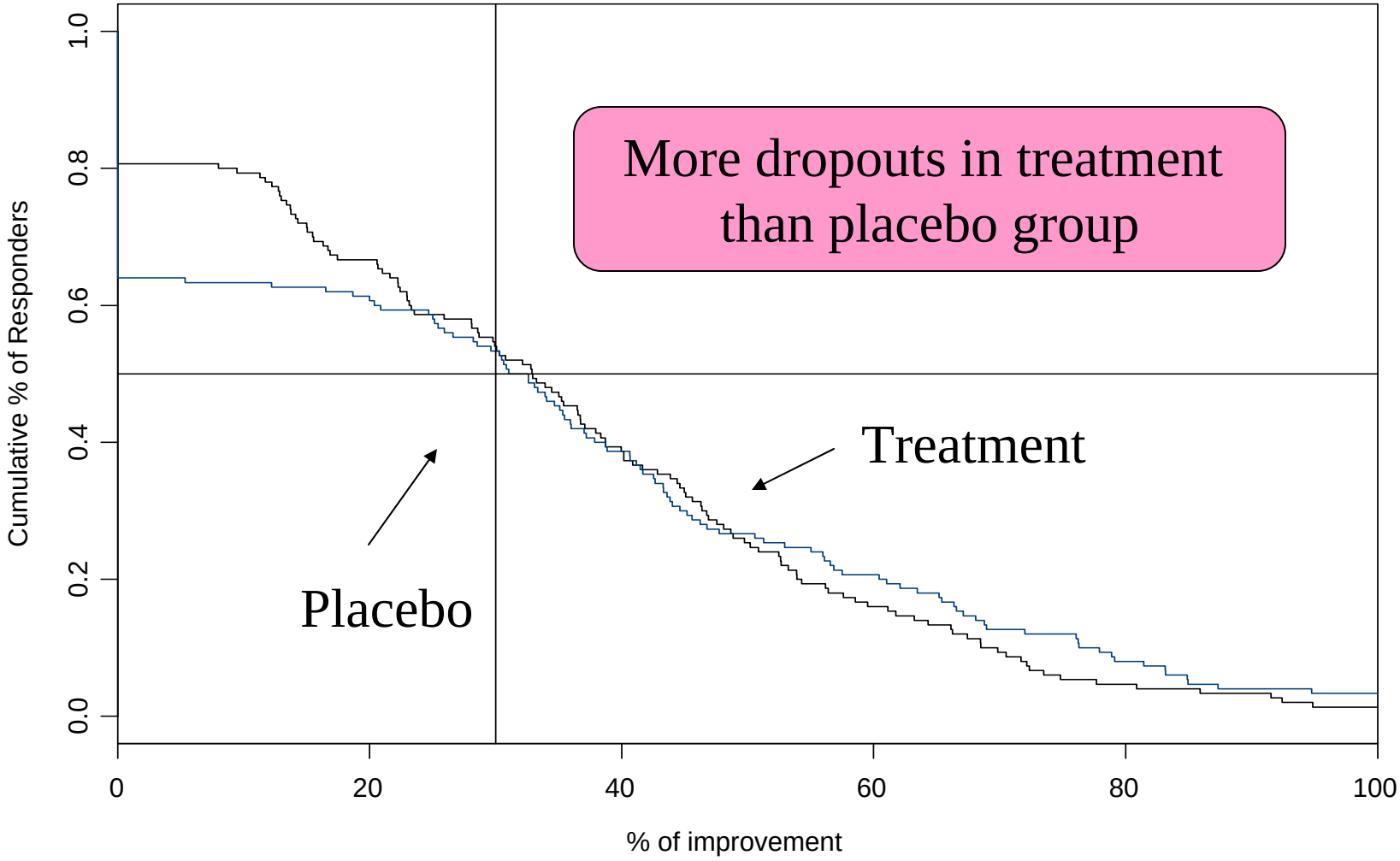
Overall 30% dropouts: Various dropout patterns



Overall 30% drop outs
Various dropout patterns



Overall 30% drop outs
Various dropout patterns



Why Does This Matter?

Impact on:

- **Sample size**
- **Ability to discern treatment group differences**
- **Overall probability of technical success**

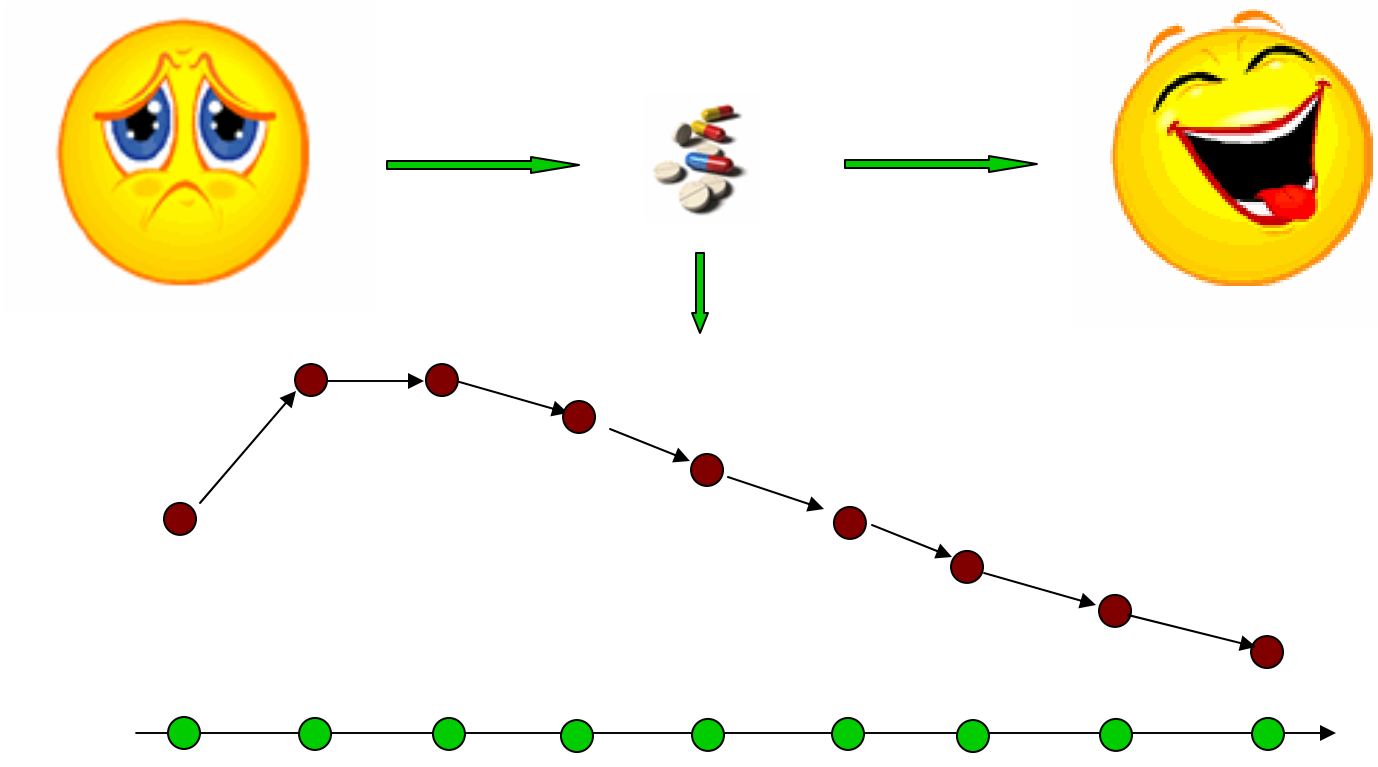
Solution?

- Study Design Need to consider:
  - Reduces discontinuation
  - Reduces factors that increase effect on placebo
    - Rescue medications use
  - Maintain subjects in the study – flexible dose studies?
  - Enriched populations?
  - Endpoint that does not require imputations

Objective for Part II

- To explore the surrogacy of "time to rescue medication" or "Total Rescue Used" in acute pain studies for the traditional primary endpoints based on the longitudinally collected pain measurements.

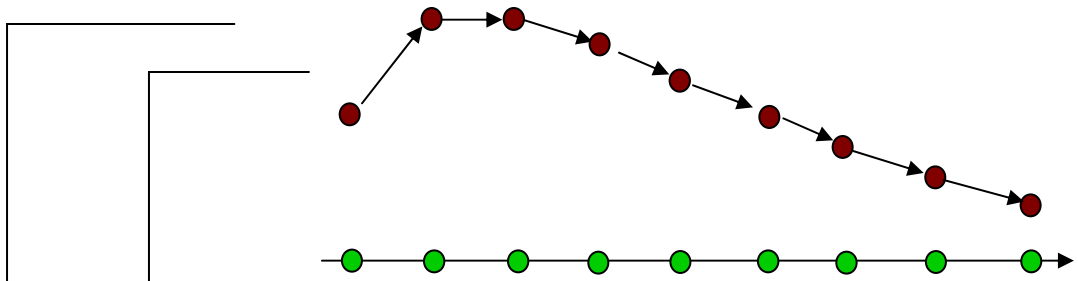
General Design of Acute Pain Studies



Scheduled Time Points

Efficacy Variables

Any one of these can be a primary variable.



Scheduled Time Points

Pain relief scores

Pain intensity scores

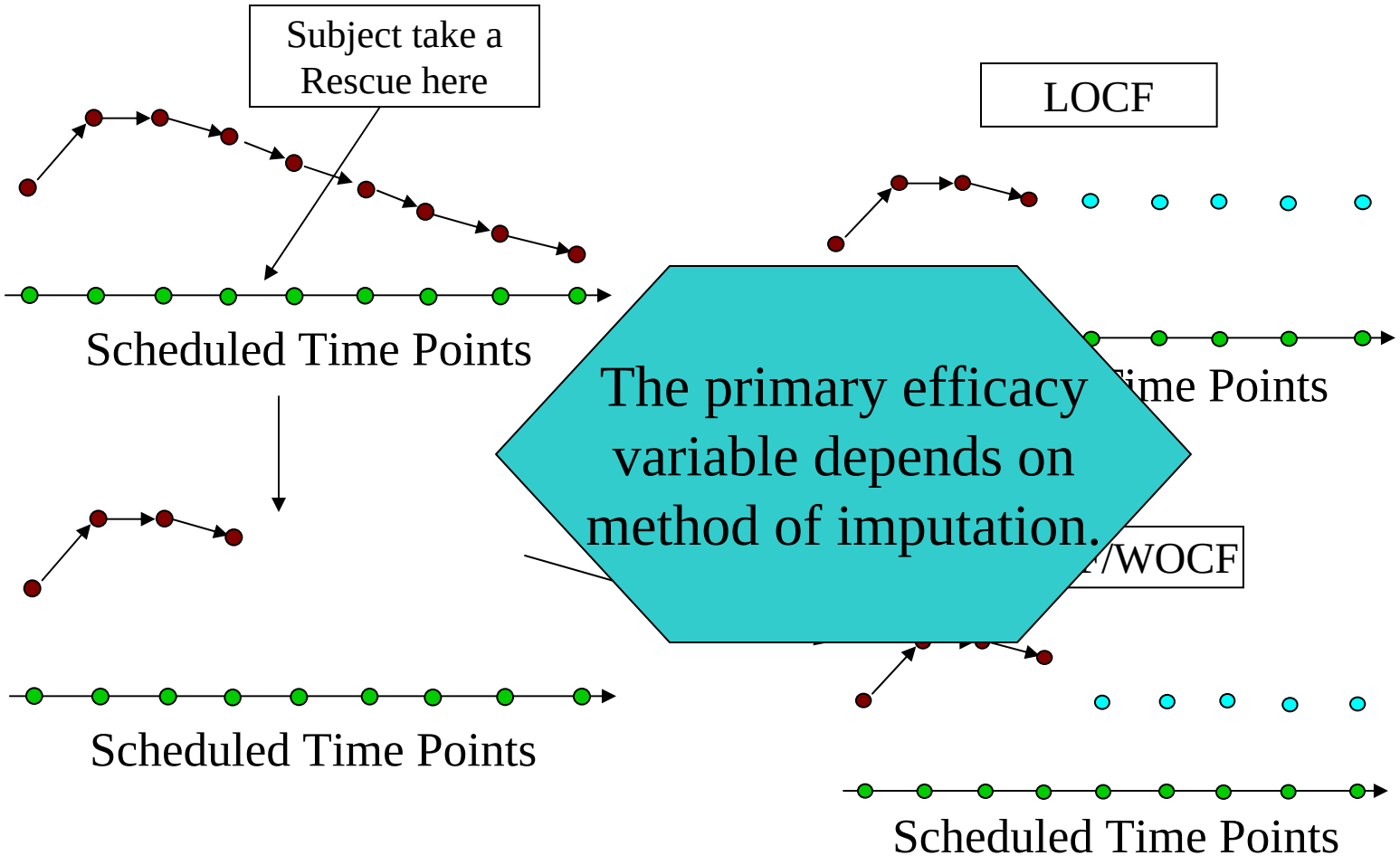
SPRID

TOTPAR

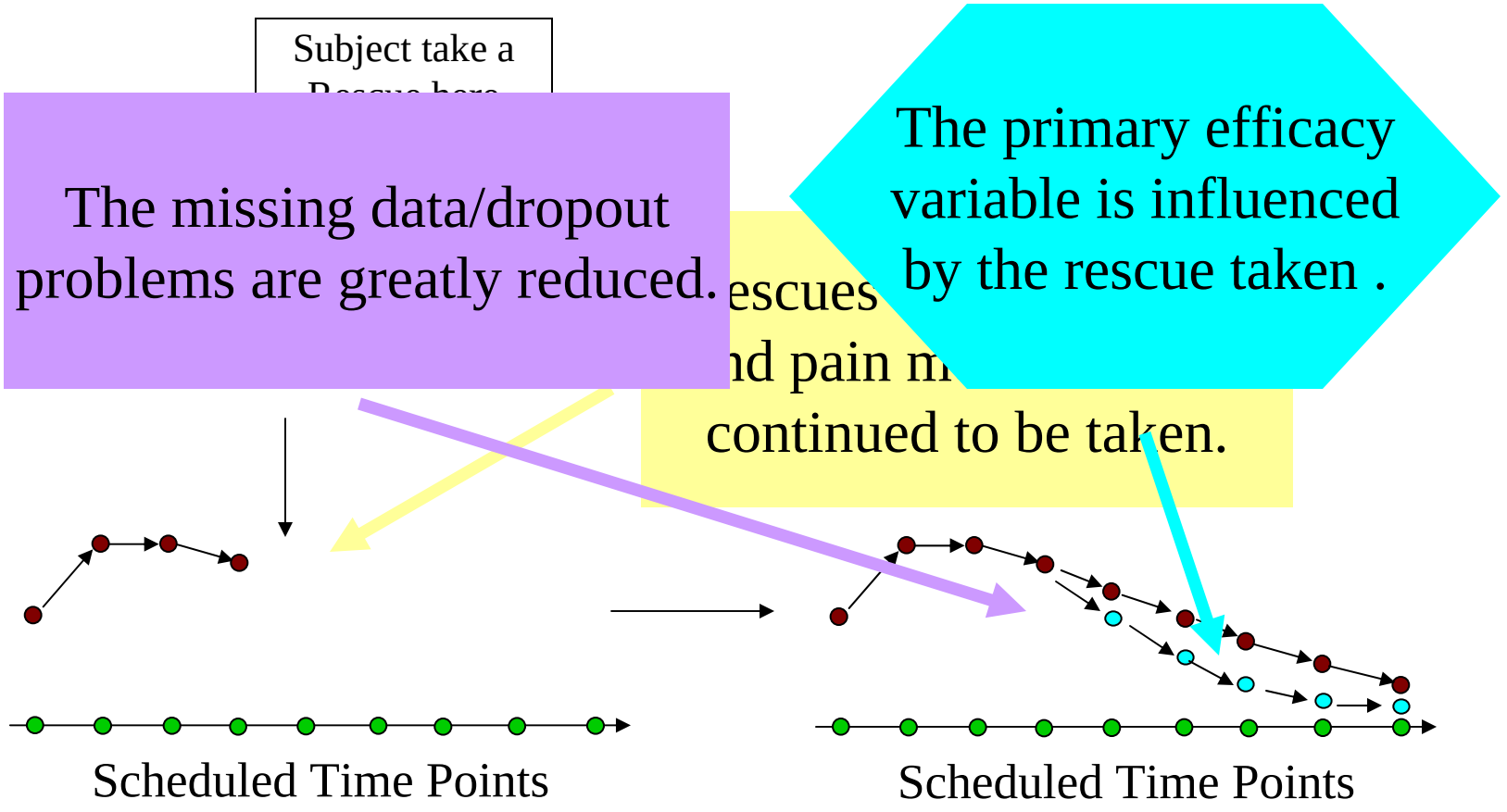
SPID

Pain intensity difference from baseline

Time to Rescue

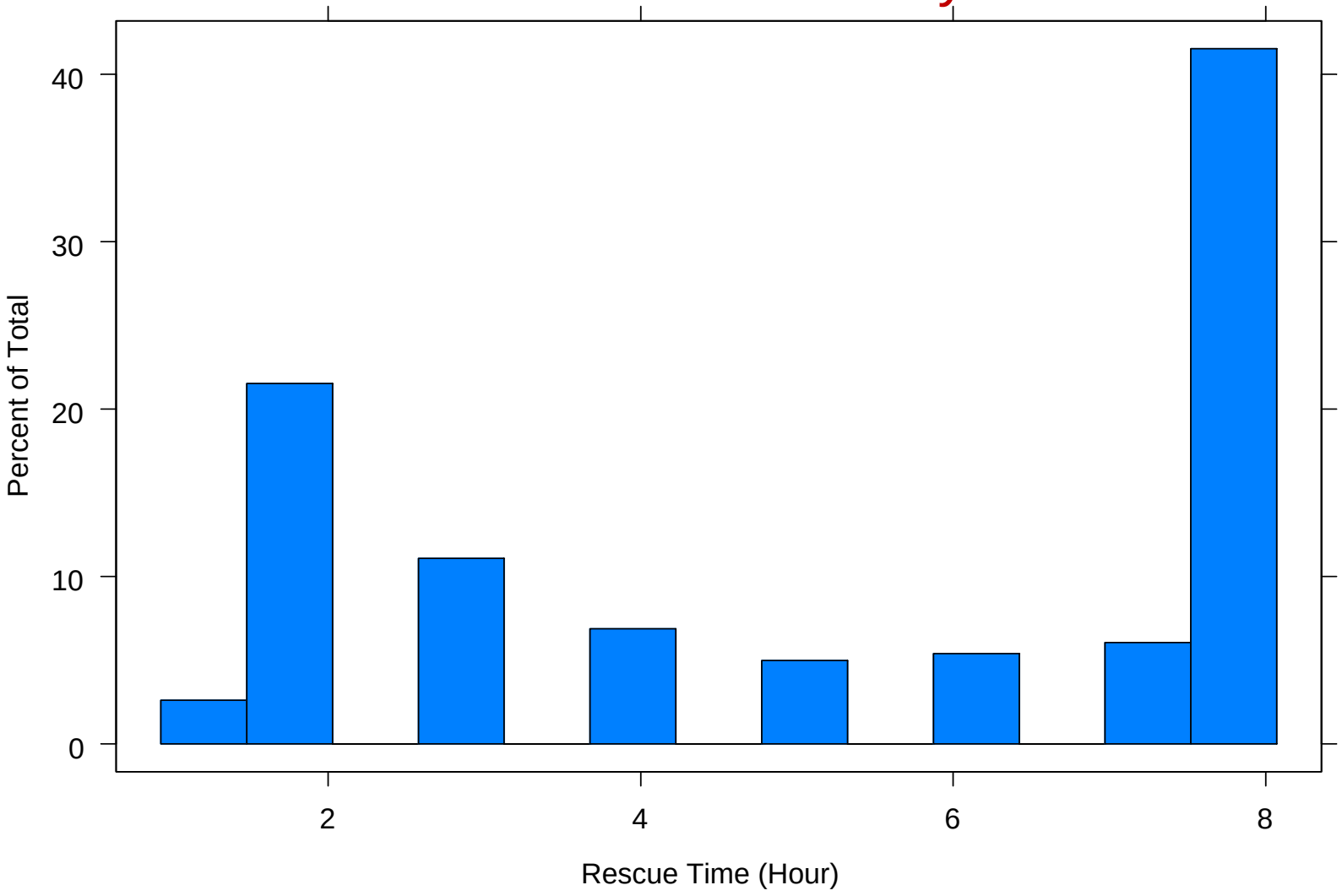


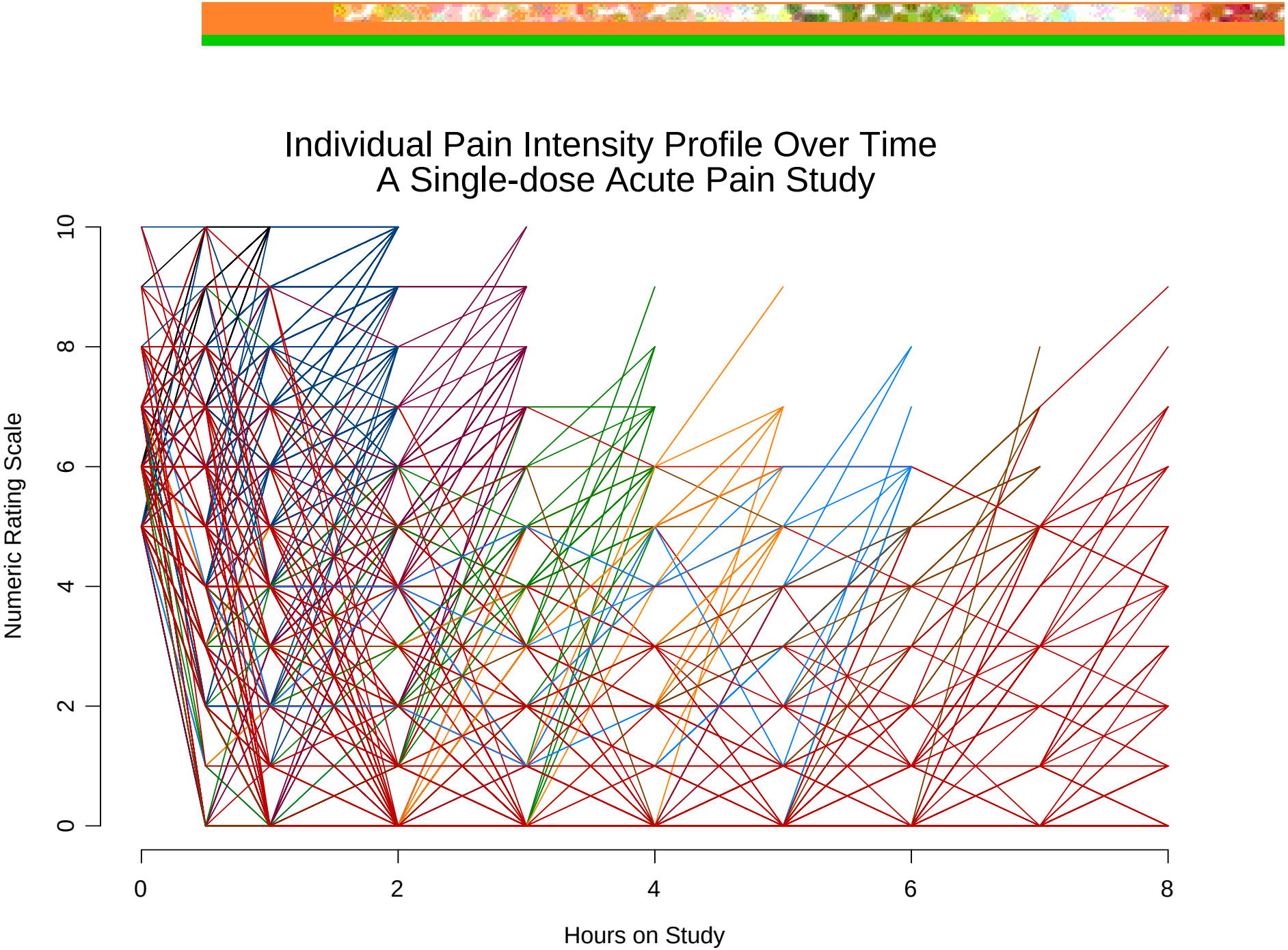
Allowing Rescue?

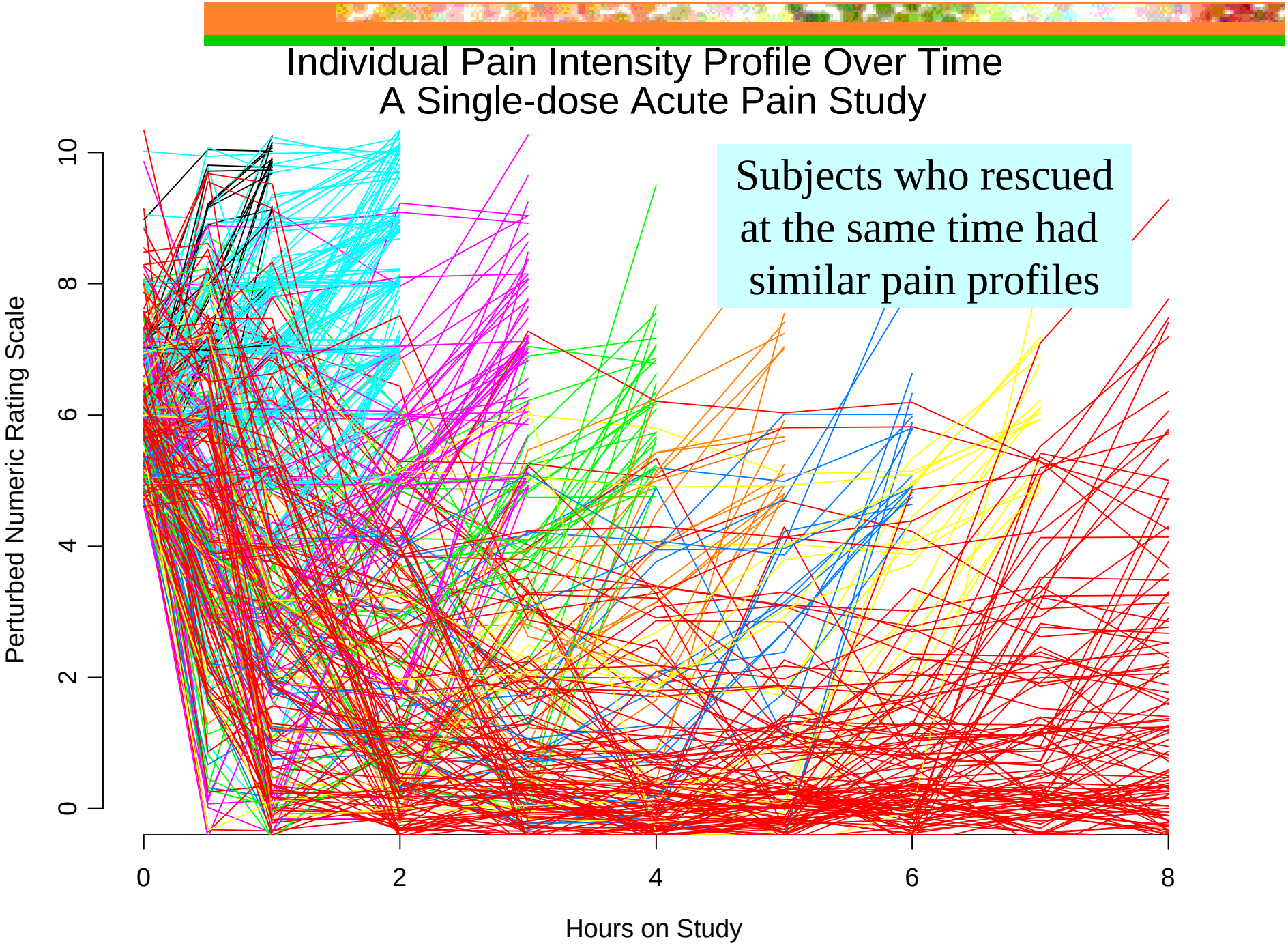


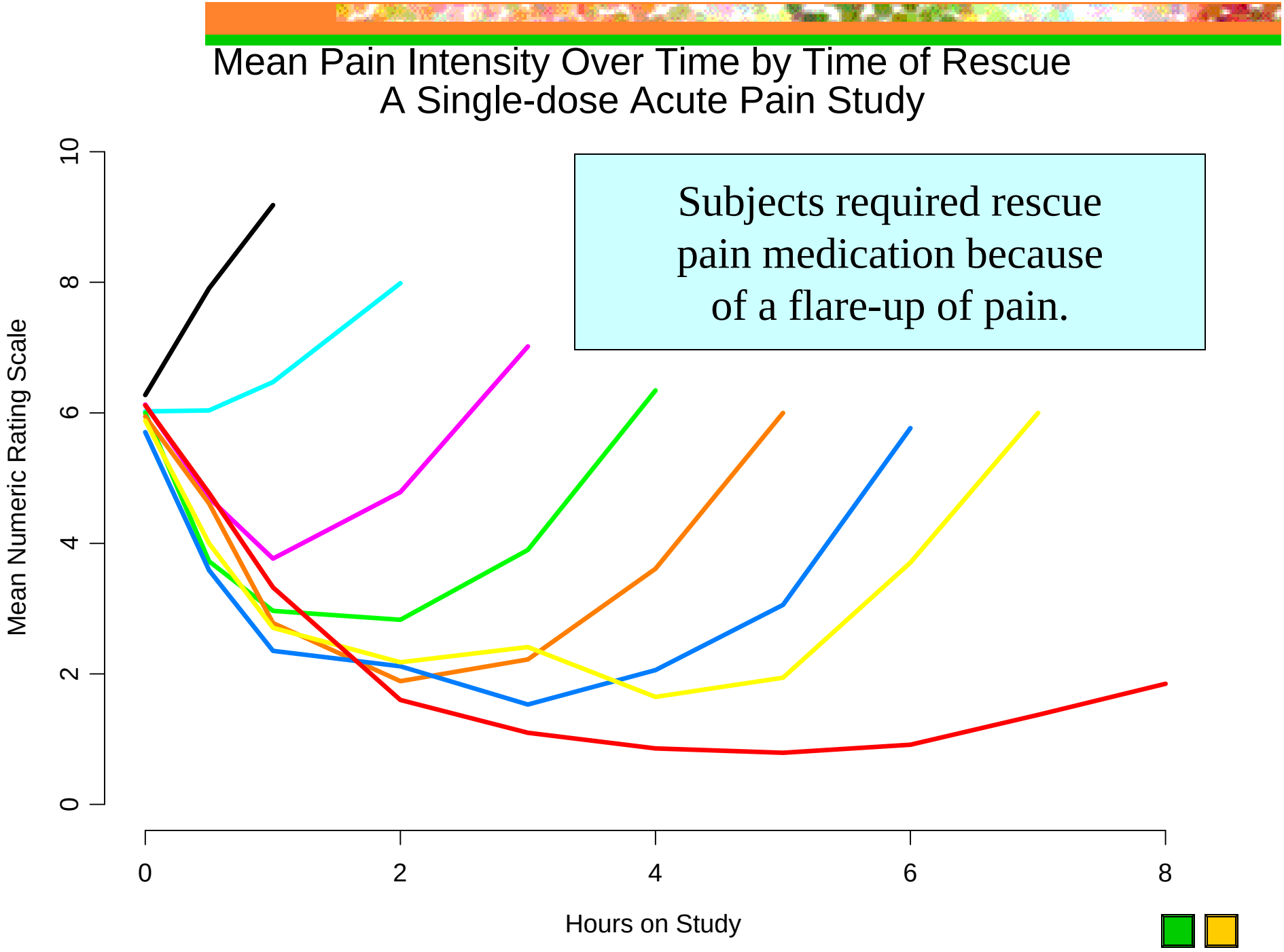
Scenario 1:
Dropout after Rescue

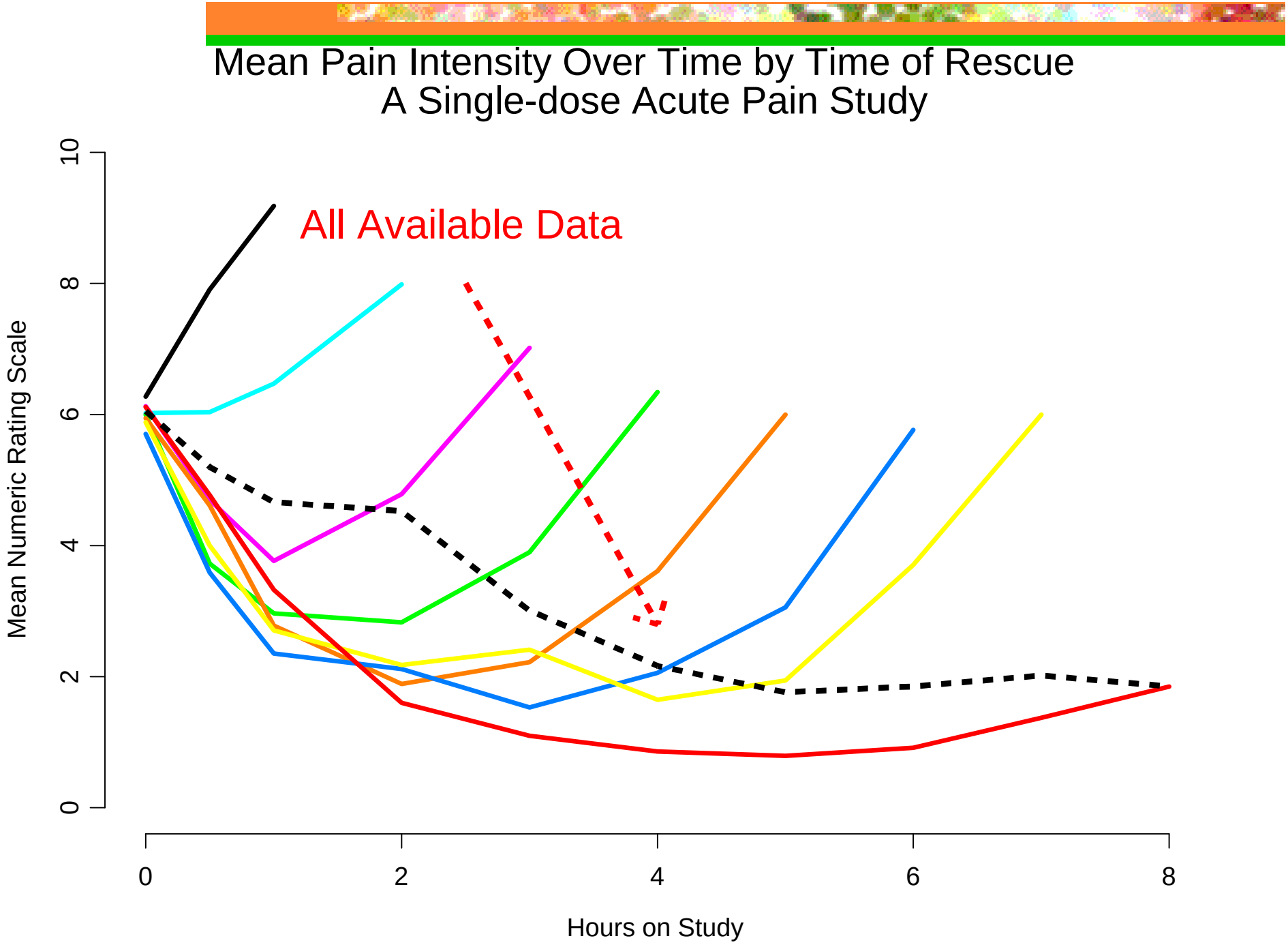
Enforced Missingness

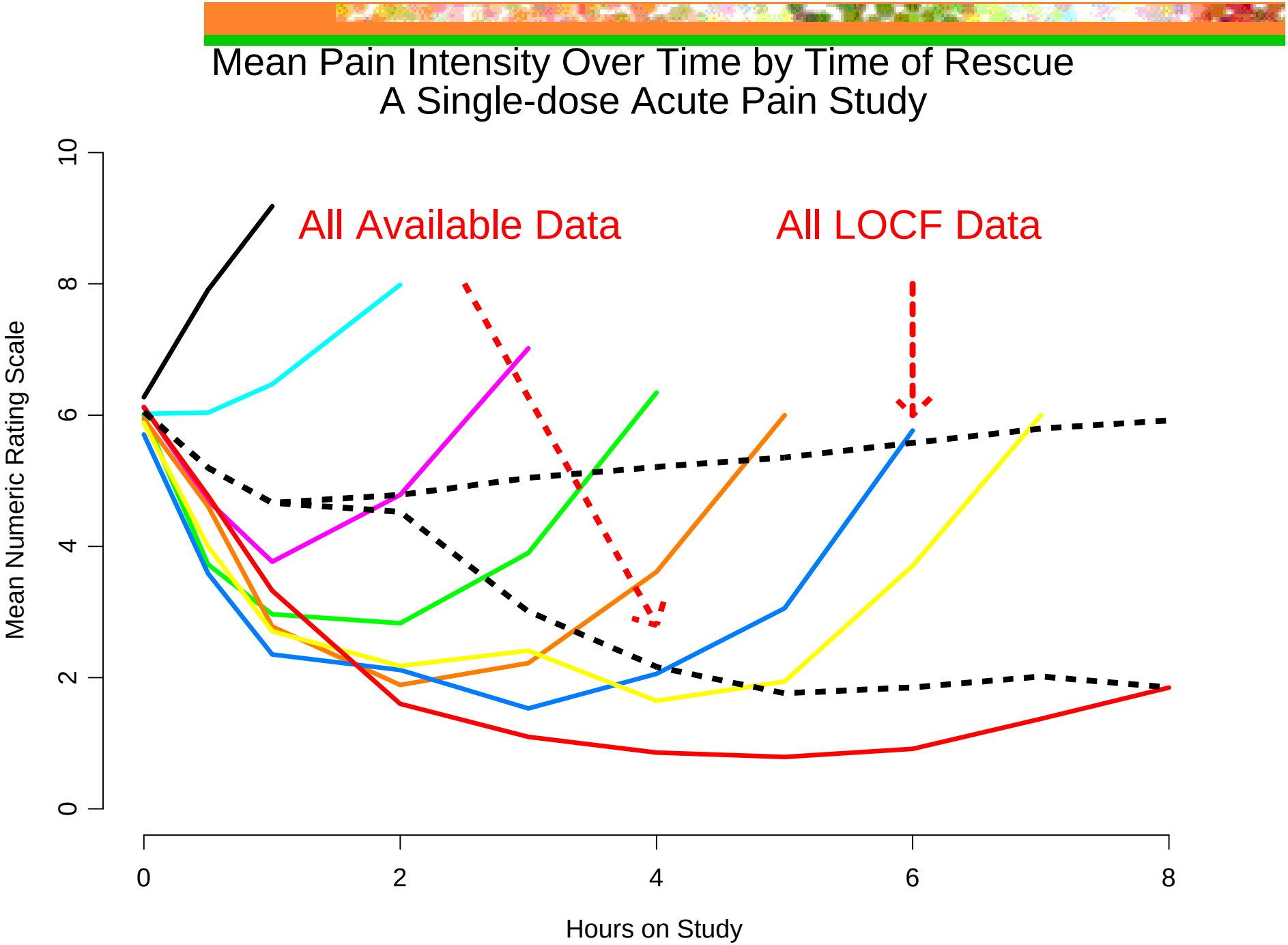

Distribution of Rescue Time
A Dental Pain Study
Percent of Total
0
10
20
30
40
2
4
6
8
Rescue Time (Hour)

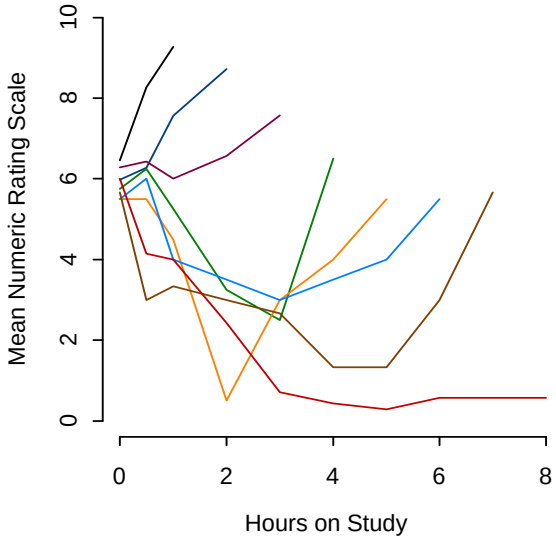

Individual Pain Intensity Profile Over Time
A Single-dose Acute Pain Study
Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study

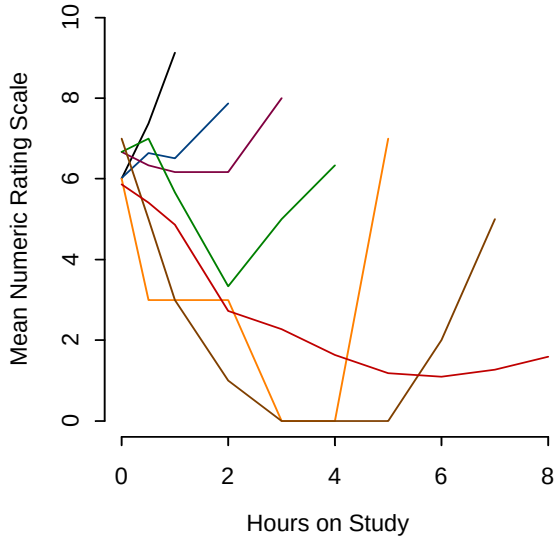

Individual Pain Intensity Profile Over Time
A Single-dose Acute Pain Study
Subjects who rescued at the same time had similar pain profiles
Perturbed Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study

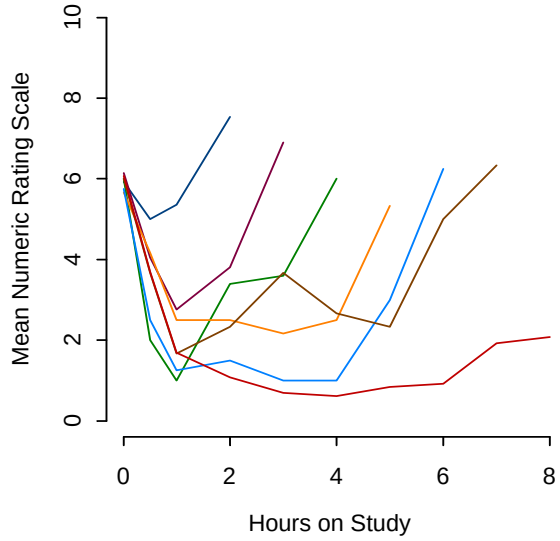

Mean Pain Intensity Over Time by Time of Rescue
A Single-dose Acute Pain Study
Subjects required rescue pain medication because of a flare-up of pain.
Mean Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study

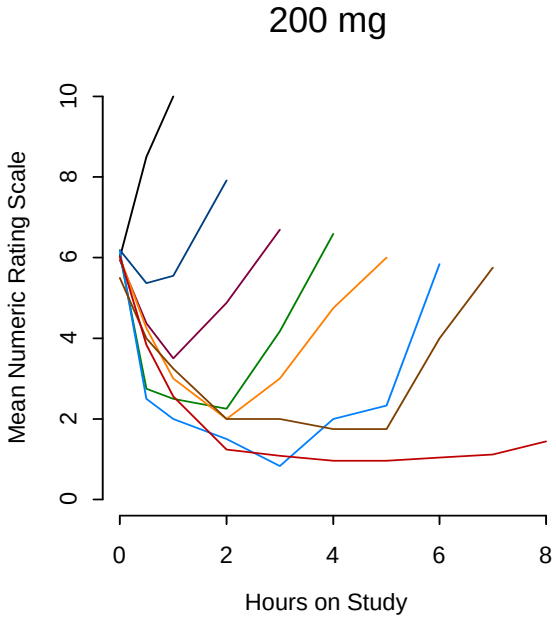

Mean Pain Intensity Over Time by Time of Rescue
A Single-dose Acute Pain Study
All Available Data
Mean Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study

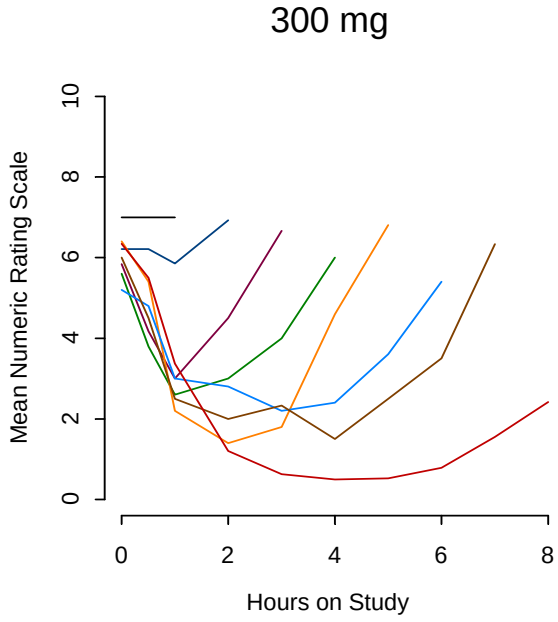

Mean Pain Intensity Over Time by Time of Rescue
A Single-dose Acute Pain Study
All Available Data
All LOCF Data
Mean Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study


0 mg
Mean Numeric Rating Scale
Hours on Study
0
2
4
6
8
10

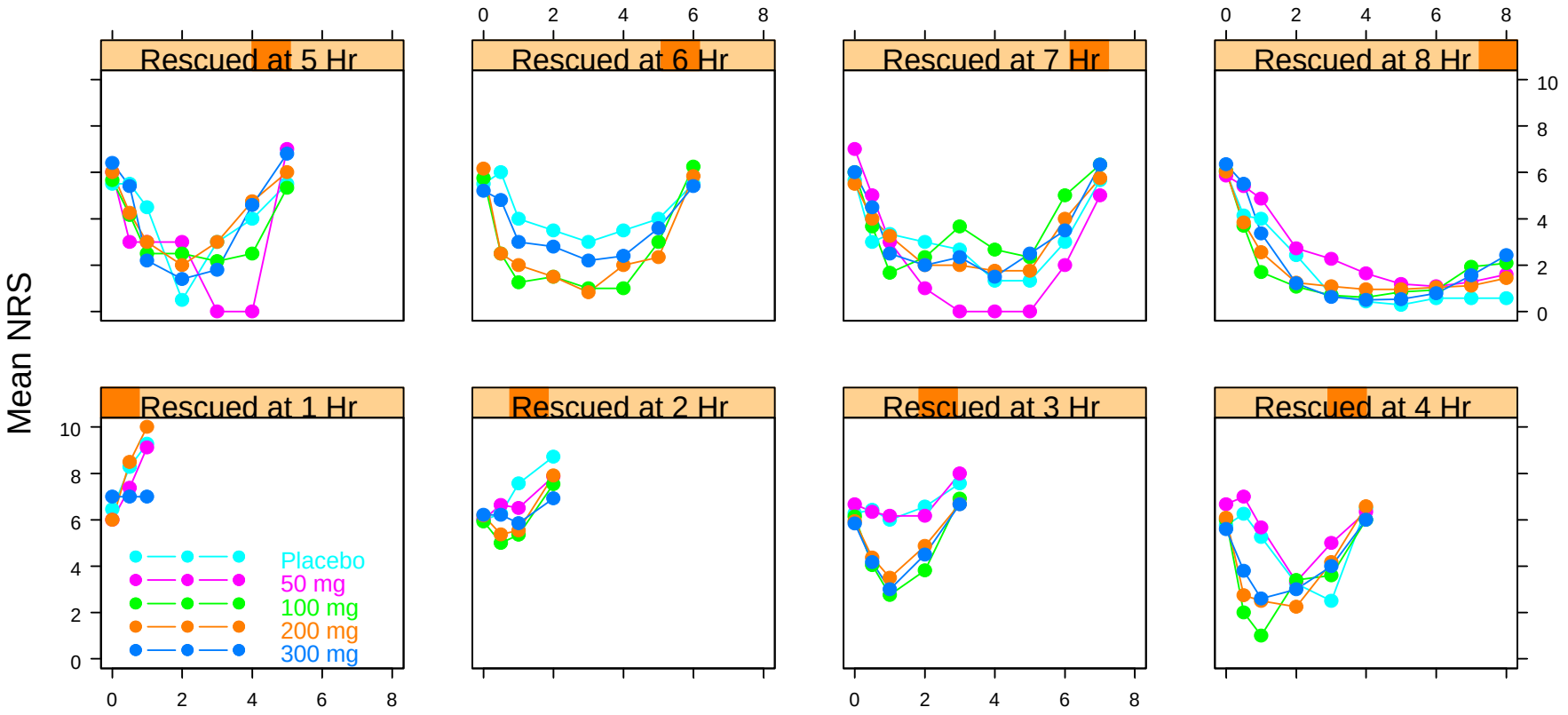

50 mg
Mean Numeric Rating Scale
Hours on Study
0
2
4
6
8
10

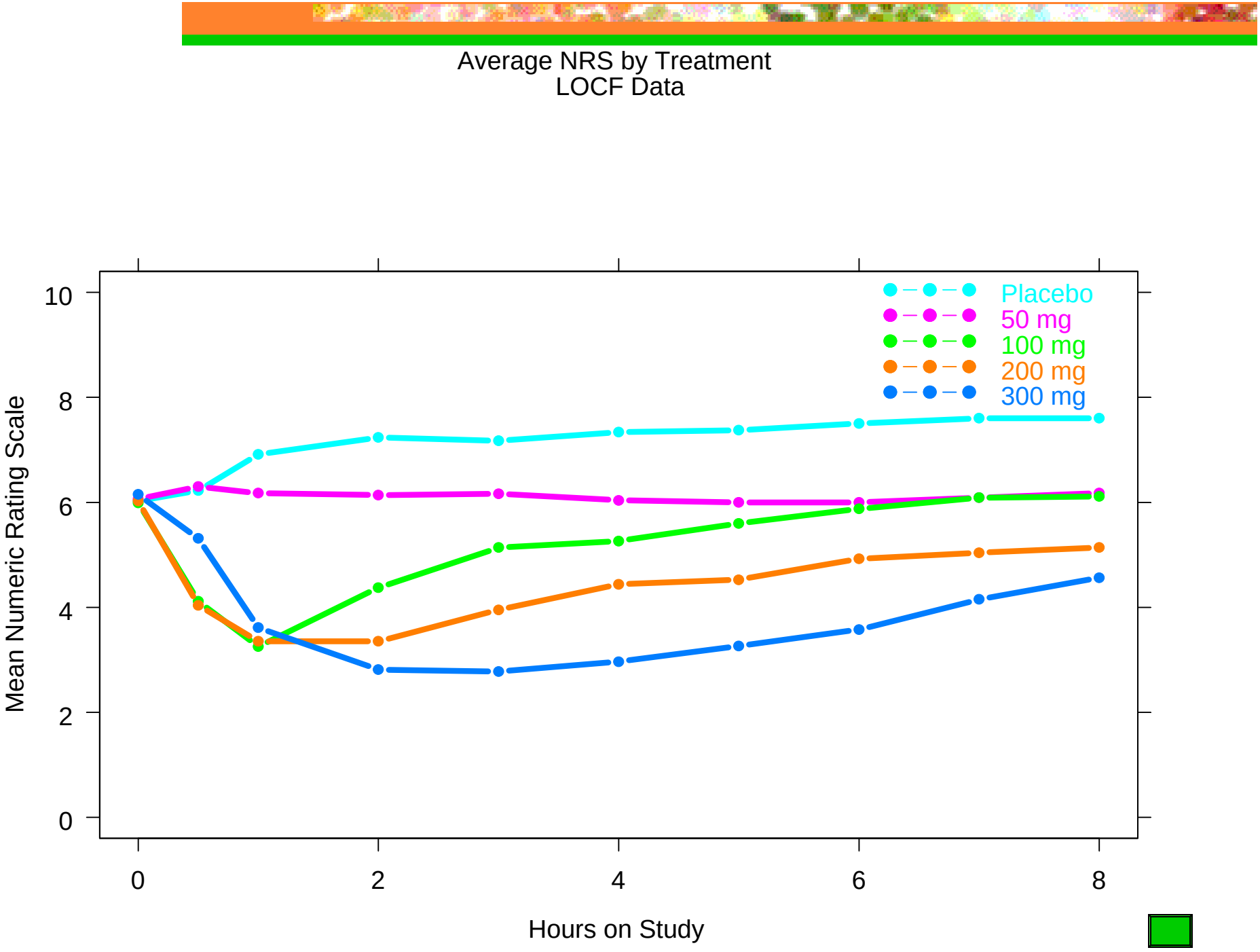

100 mg
Mean Numeric Rating Scale
Hours on Study
0
2
4
6
8
10

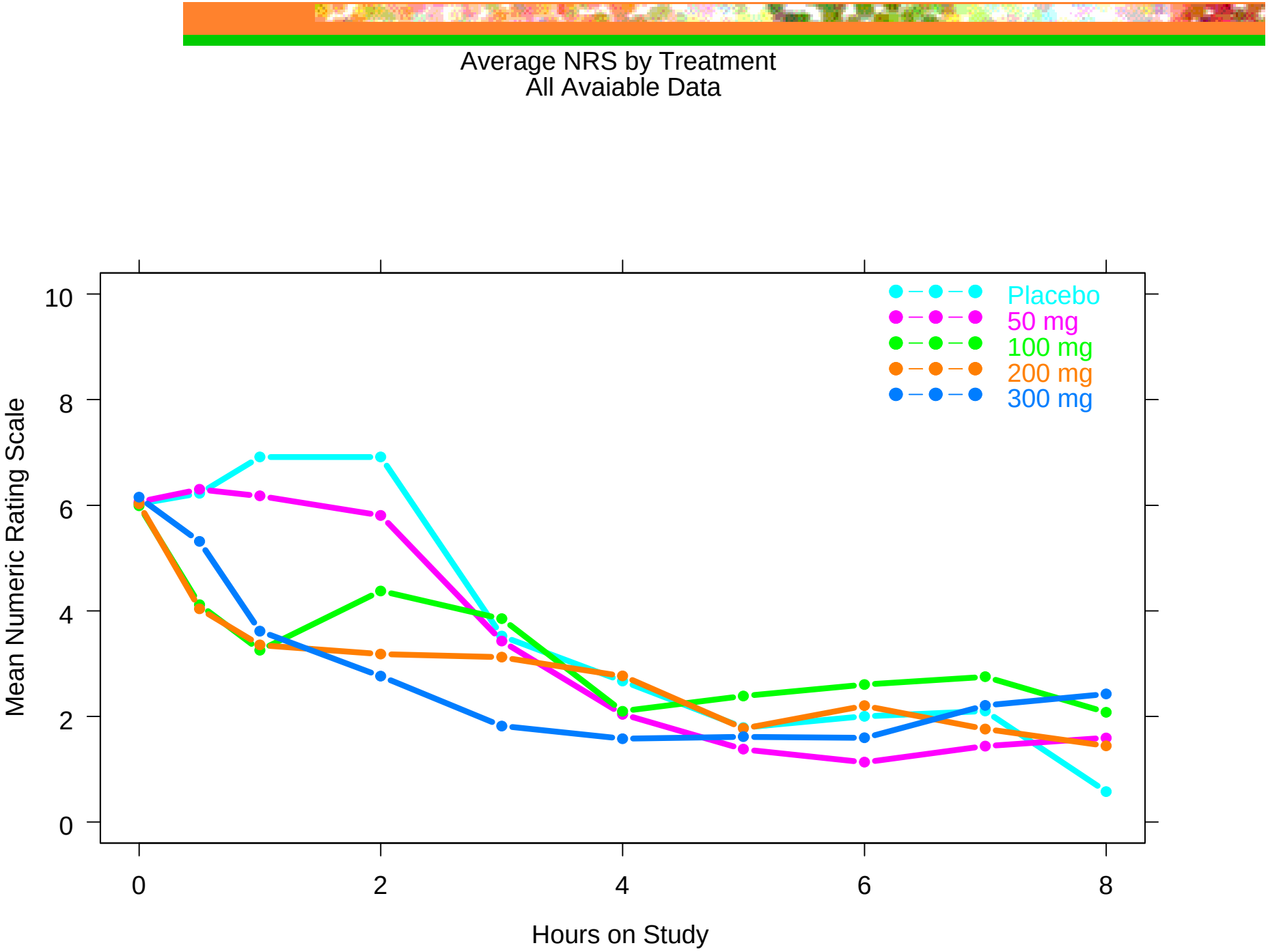

200 mg
Mean Numeric Rating Scale
Hours on Study
0
2
4
6
8
10

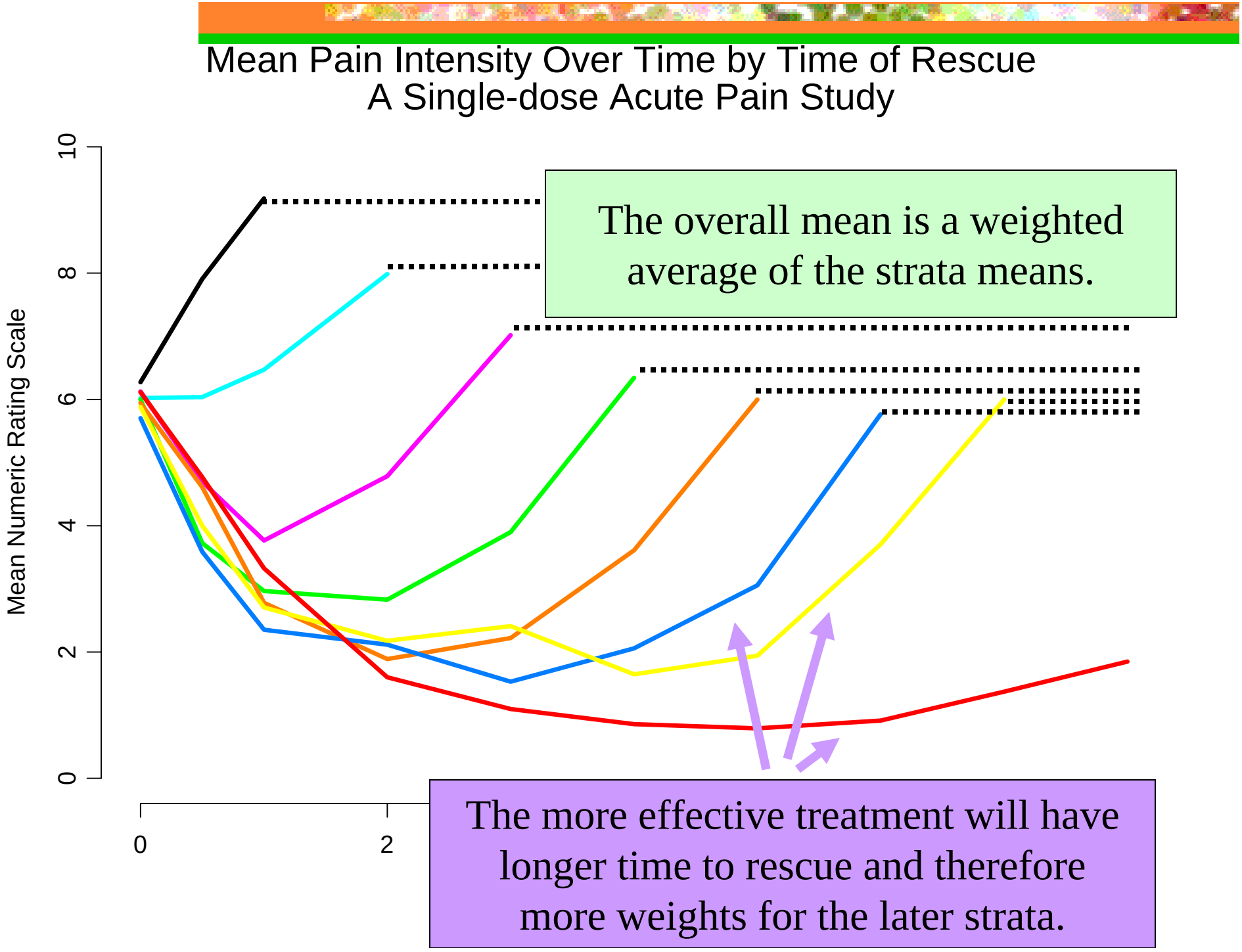

300 mg
Mean Numeric Rating Scale
Hours on Study
0
2
4
6
8
10

A Single-dose Acute Pain Trial

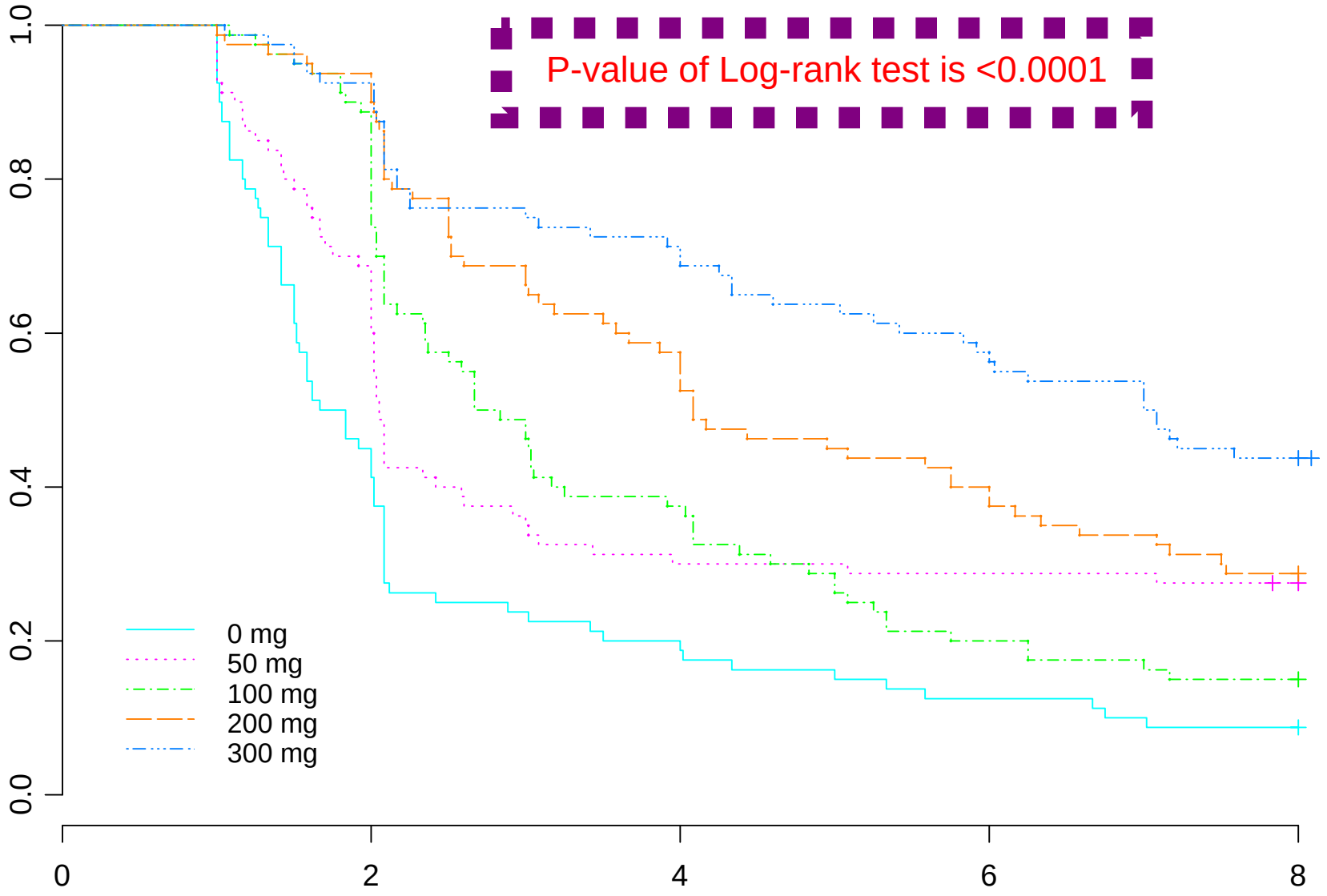



Average NRS by Treatment
LOCF Data
Placebo
50 mg
100 mg
200 mg
300 mg
Mean Numeric Rating Scale
0
2
4
6
8
10
Hours on Study

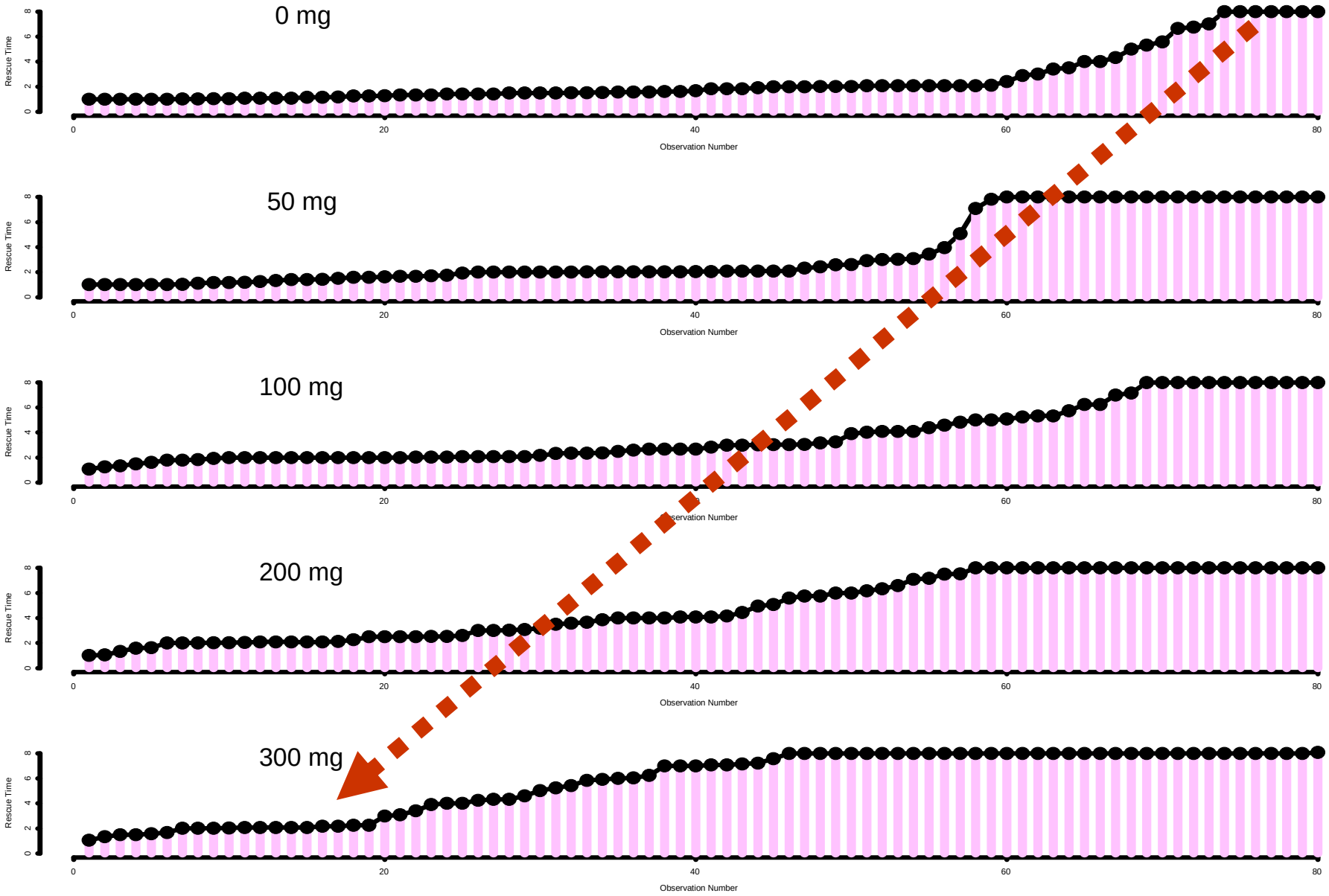

Average NRS by Treatment
All Avaiable Data
Placebo
50 mg
100 mg
200 mg
300 mg
Mean Numeric Rating Scale
0
2
4
6
8
10
Hours on Study
0
2
4
6
8


Mean Pain Intensity Over Time by Time of Rescue
A Single-dose Acute Pain Study
Mean Numeric Rating Scale
0
2
4
6
8
10
0
2
The overall mean is a weighted average of the strata means.
The more effective treatment will have longer time to rescue and therefore more weights for the later strata.

Kaplan-Meier Survival Curves for Time to Rescue
A Single-dose Acute Pain Study



Distribution of Time to Rescue



The Time to Rescue Behaves as a Surrogate

According to Prentice (1989):

S (the time to rescue) is a surrogate of T(t) (pain scores) if

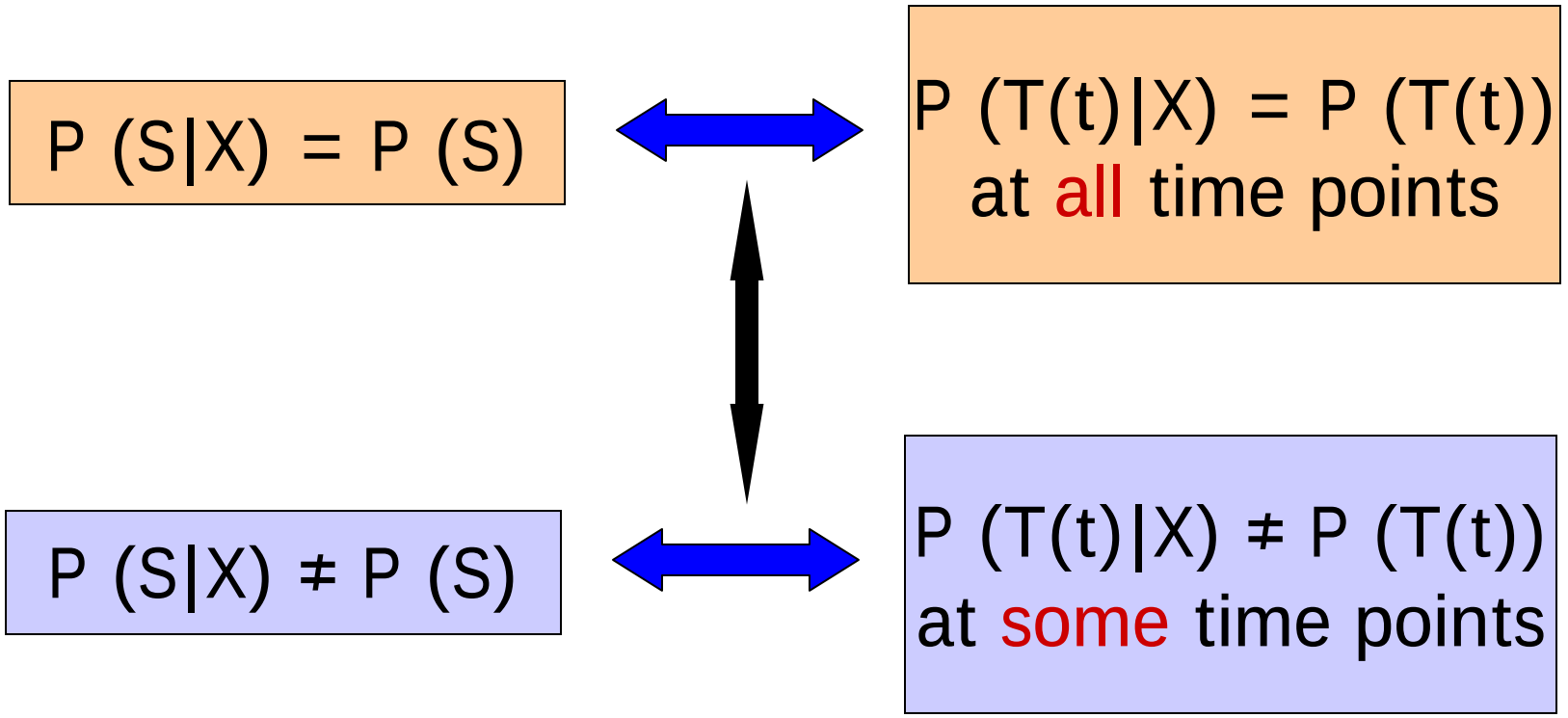
$$P (T(t) | \cancel{X,} S) = P (T(t) | S)$$

at all time points of t

where X denotes treatment

Equivalent Inferences

T(t) and S give the same inference on X



What is required?

$P (T(t) \mid X, S) = P (T(t) \mid S)$

at all time points of t

$P (T(t)|X) \neq P (T(t))$ at all time points

$P (T(t)|S) \neq P (T(t))$ at some time points

$P (S|X) \neq P (S)$

What do we expect to see in models?

(1) Model P (T(t) | X, S)

at all time points of t

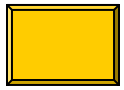
Coefficient of X should be small.

(2) Model P (T(t)|X) at all time points

(3) Model P (T(t)|S)

(4) Model P (S|X)

Coefficient of X should be big.



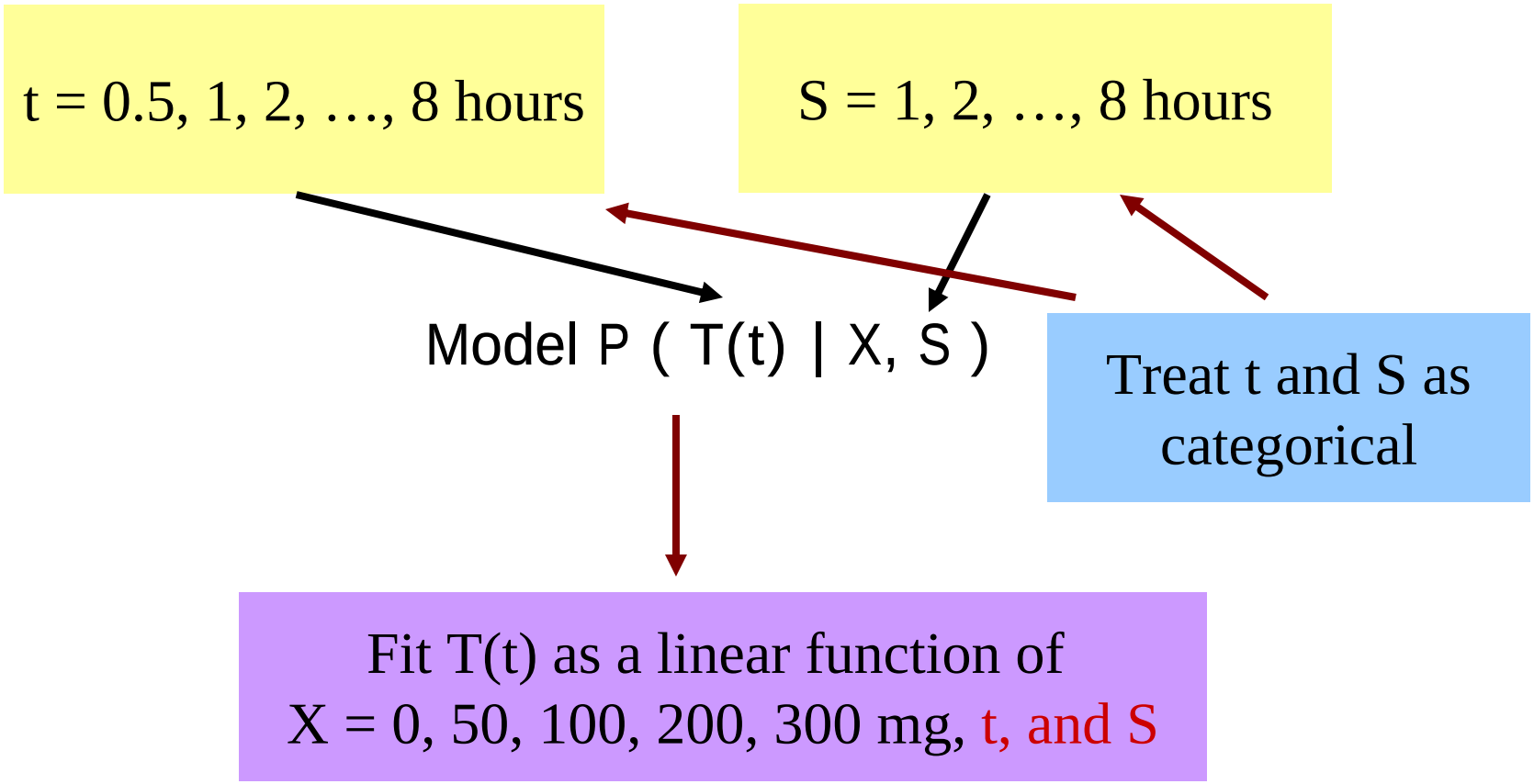
Proportion of Treatment Effect Explained (PTE)

PTE =

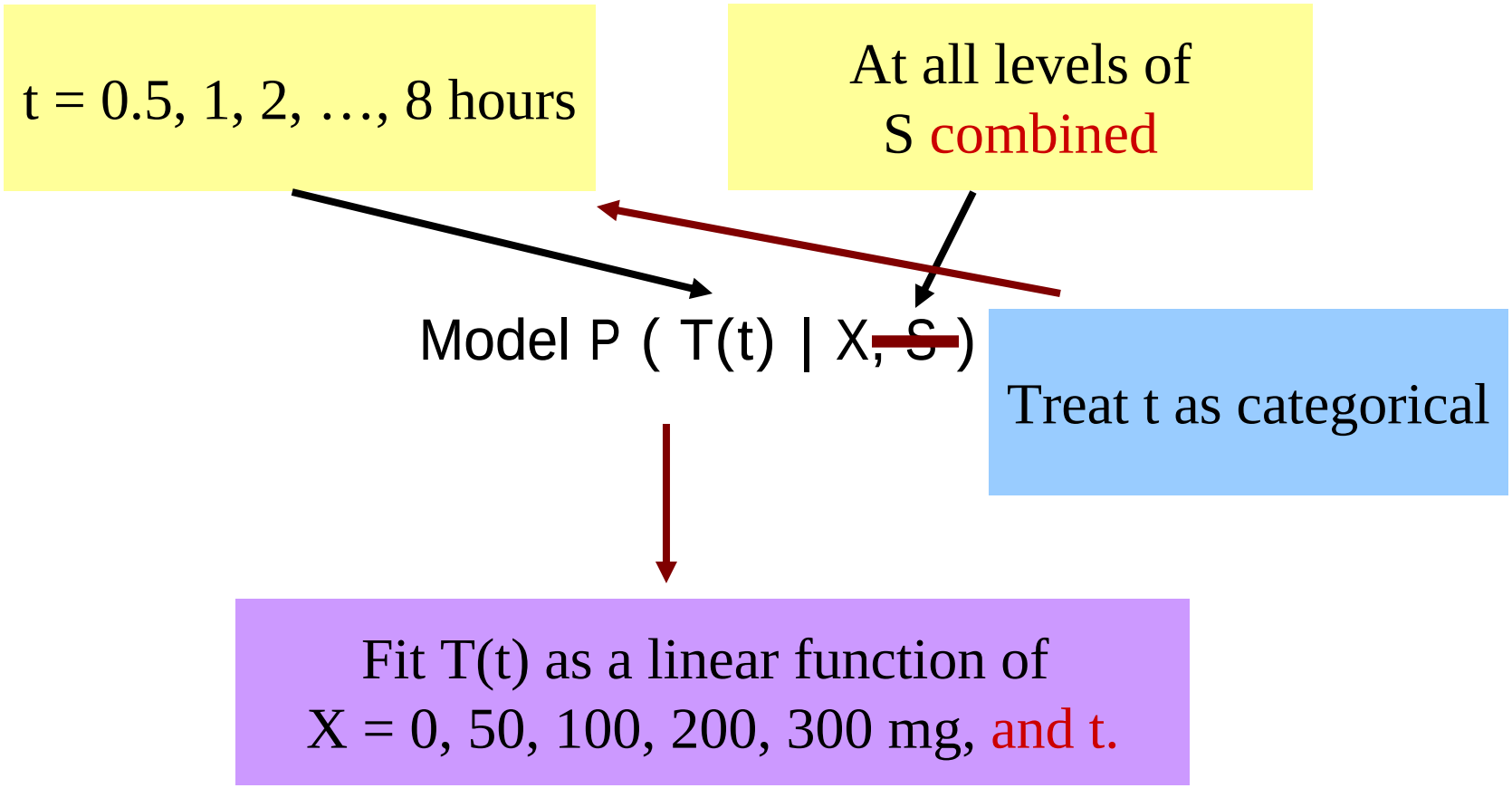
(coef of X in model (2)- coef of X in model (1))
/ (coef of X in model (2))

Freedman, L. and Graubard, B. (1992)

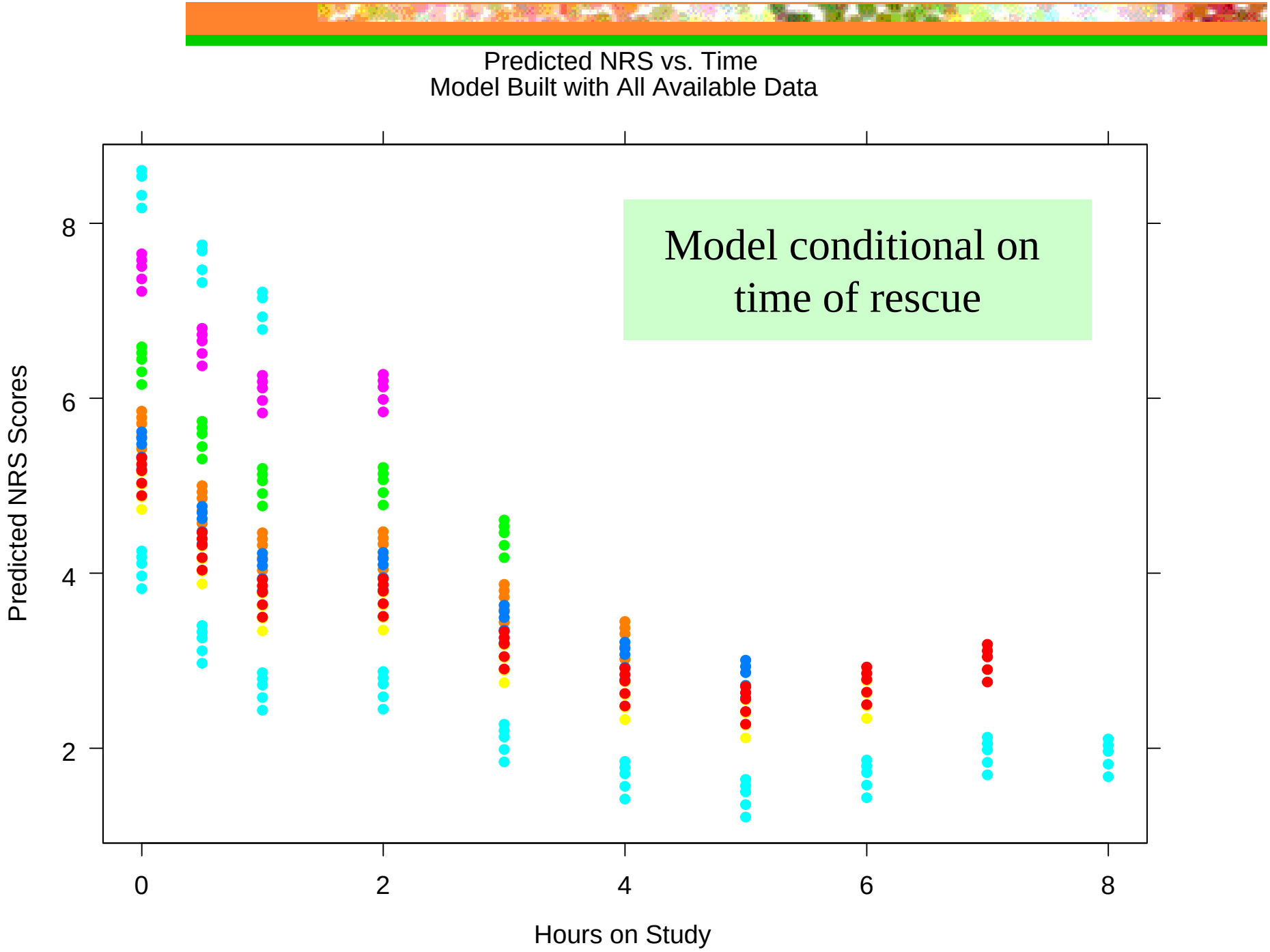
The First Model

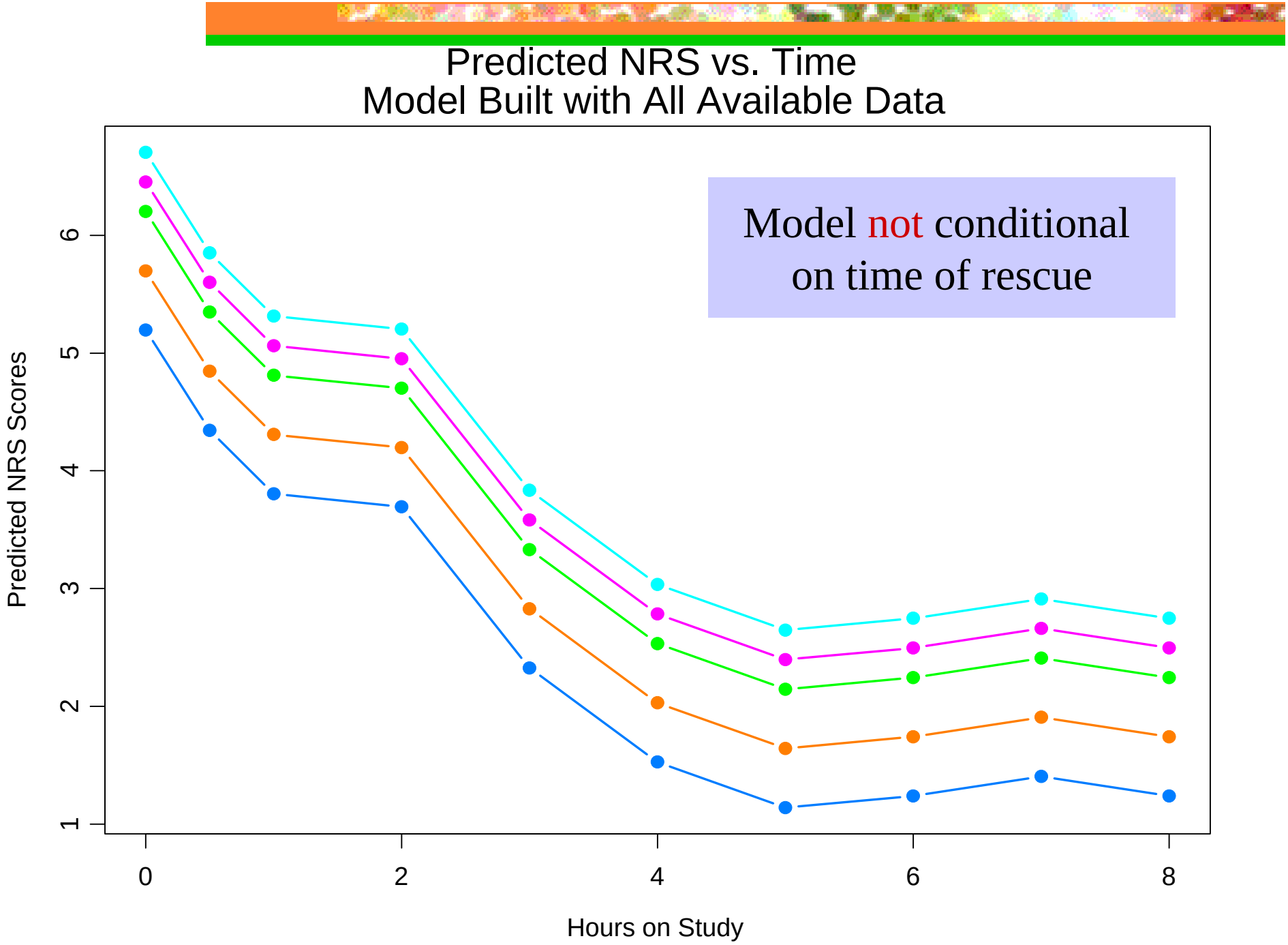


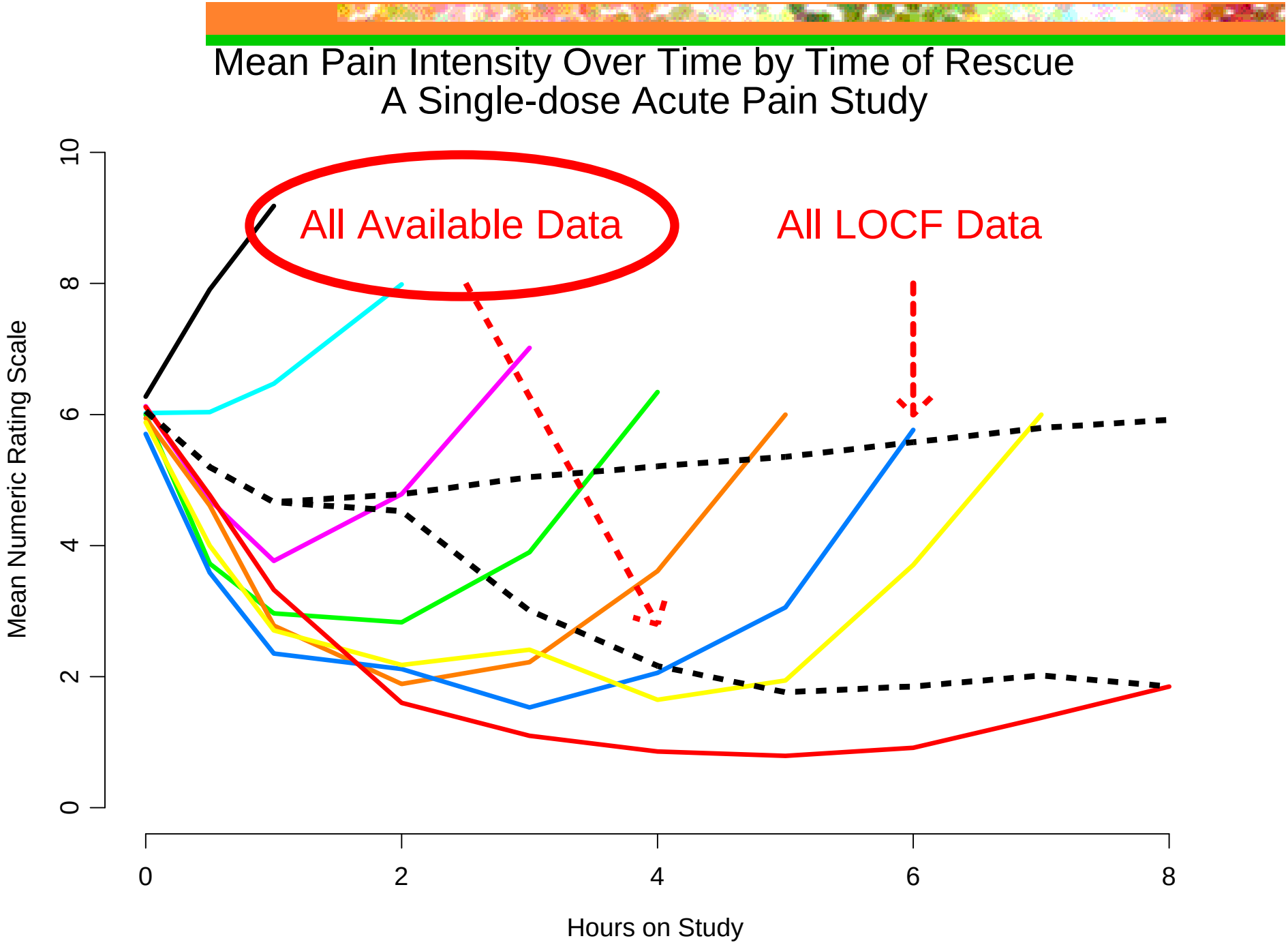
The Second Model



Fitting the models using the all-available data

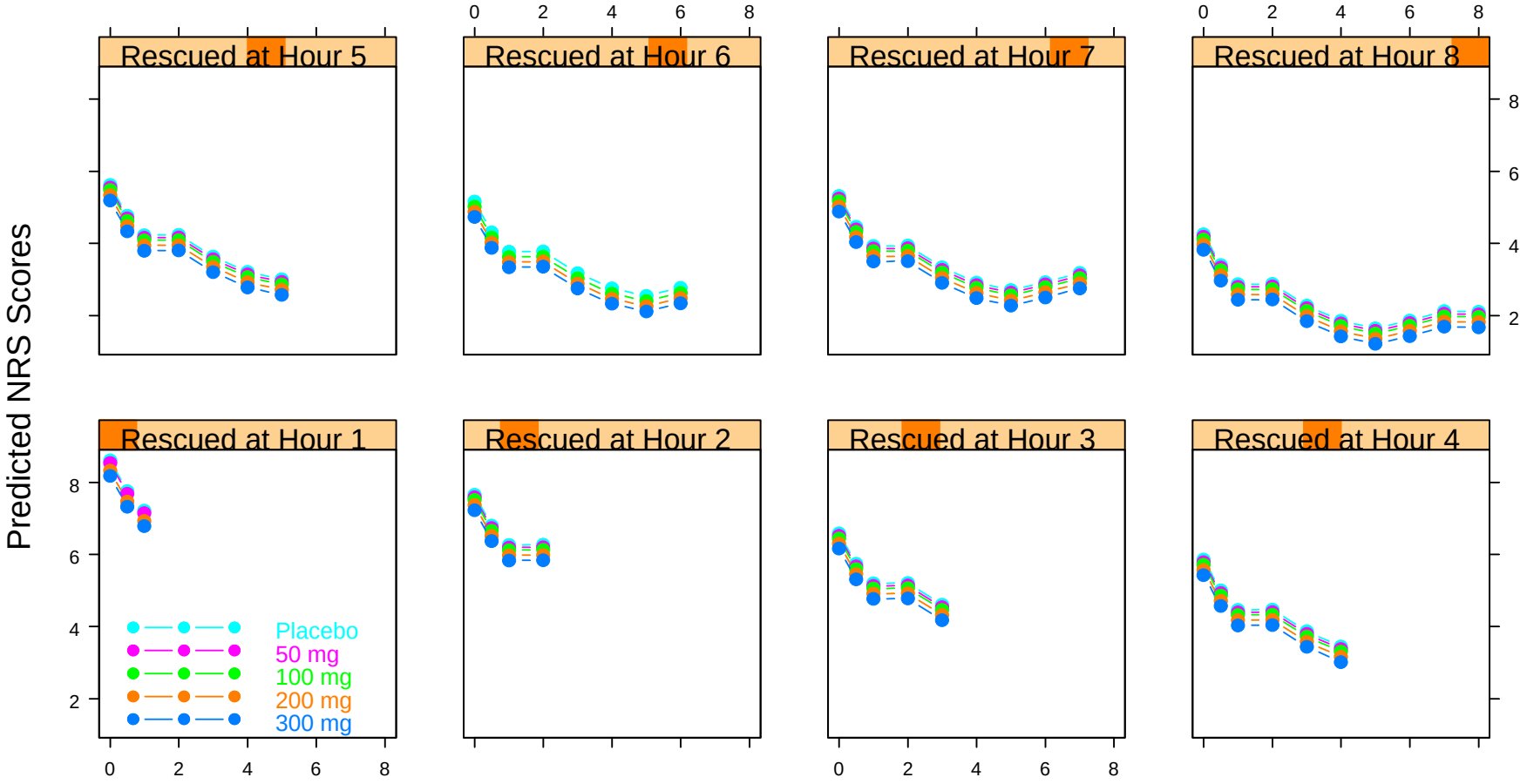

Predicted NRS vs. Time
Model Built with All Available Data
Model conditional on time of rescue
Predicted NRS Scores
Hours on Study
2
4
6
8
0
2
4
6
8


Predicted NRS vs. Time
Model Built with All Available Data
Model not conditional on time of rescue
Predicted NRS Scores
1
2
3
4
5
6
0
2
4
6
8
Hours on Study


Mean Pain Intensity Over Time by Time of Rescue
A Single-dose Acute Pain Study
All Available Data
All LOCF Data
Mean Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study

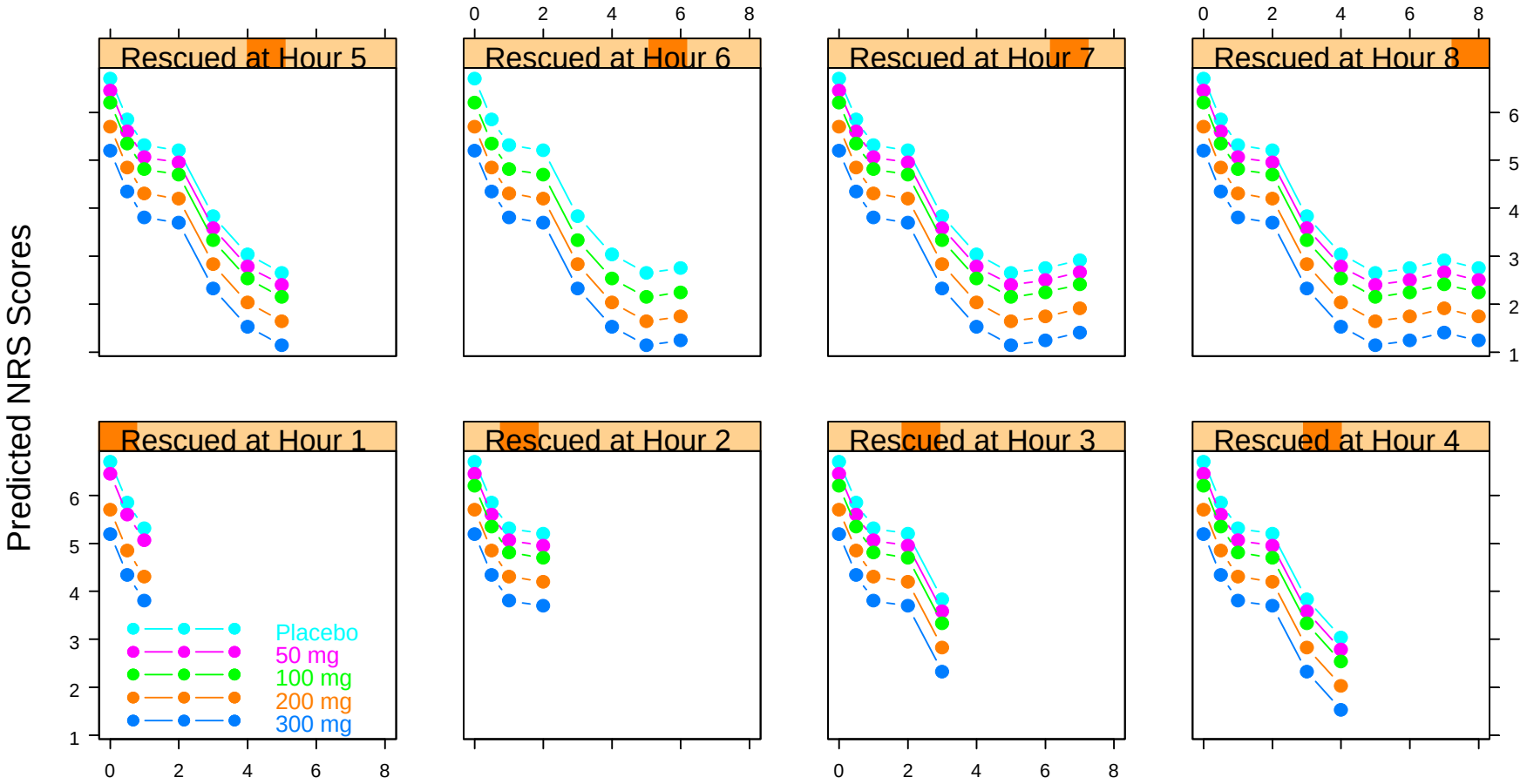
Predicted NRS vs. Time
Model Built with All Available Data

Model conditional on time of rescue

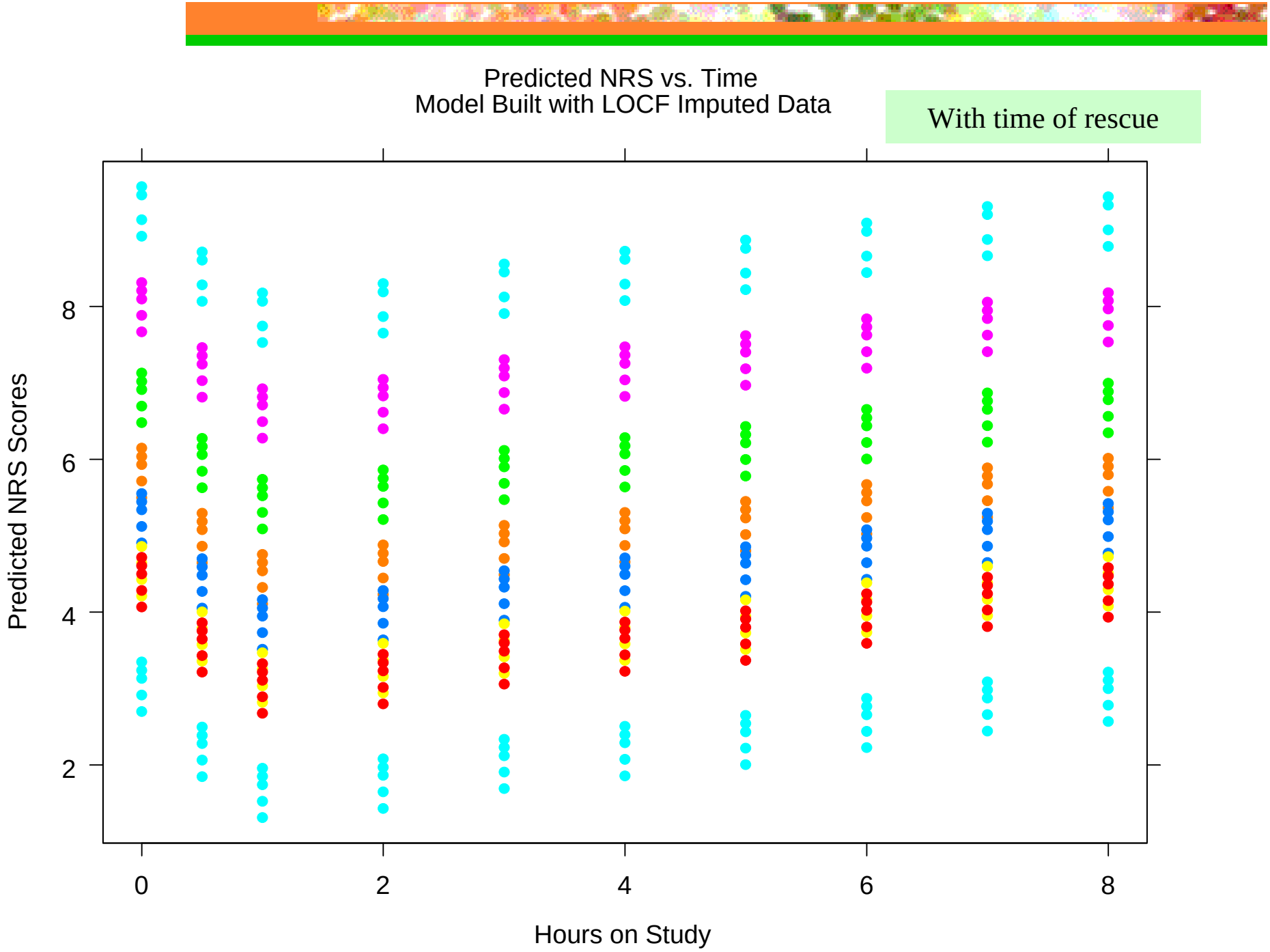


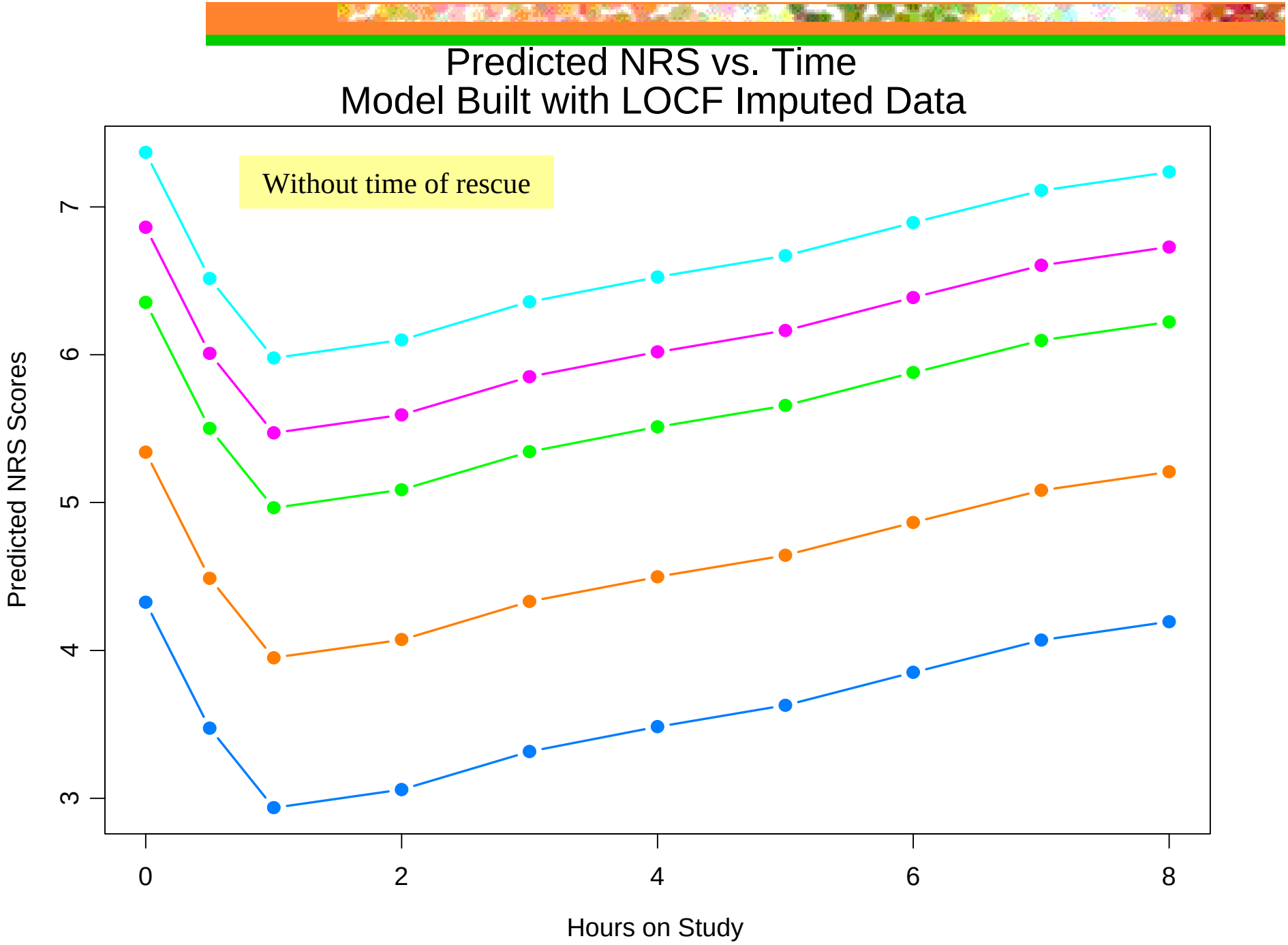
Model not conditional on time of rescue

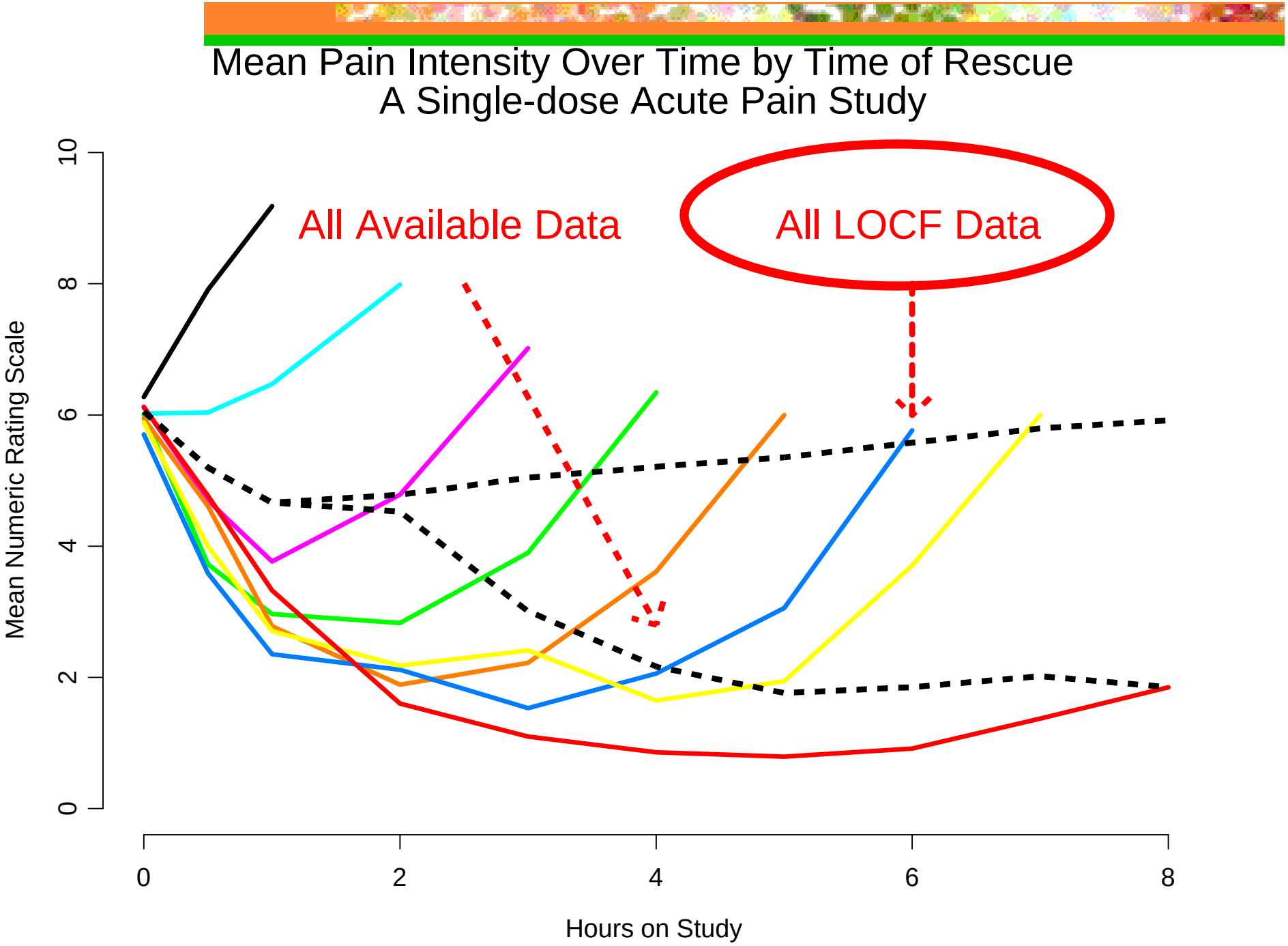
Predicted NRS vs. Time
Model Built with All Available Data



Fitting the models using the LOCF-imputed data

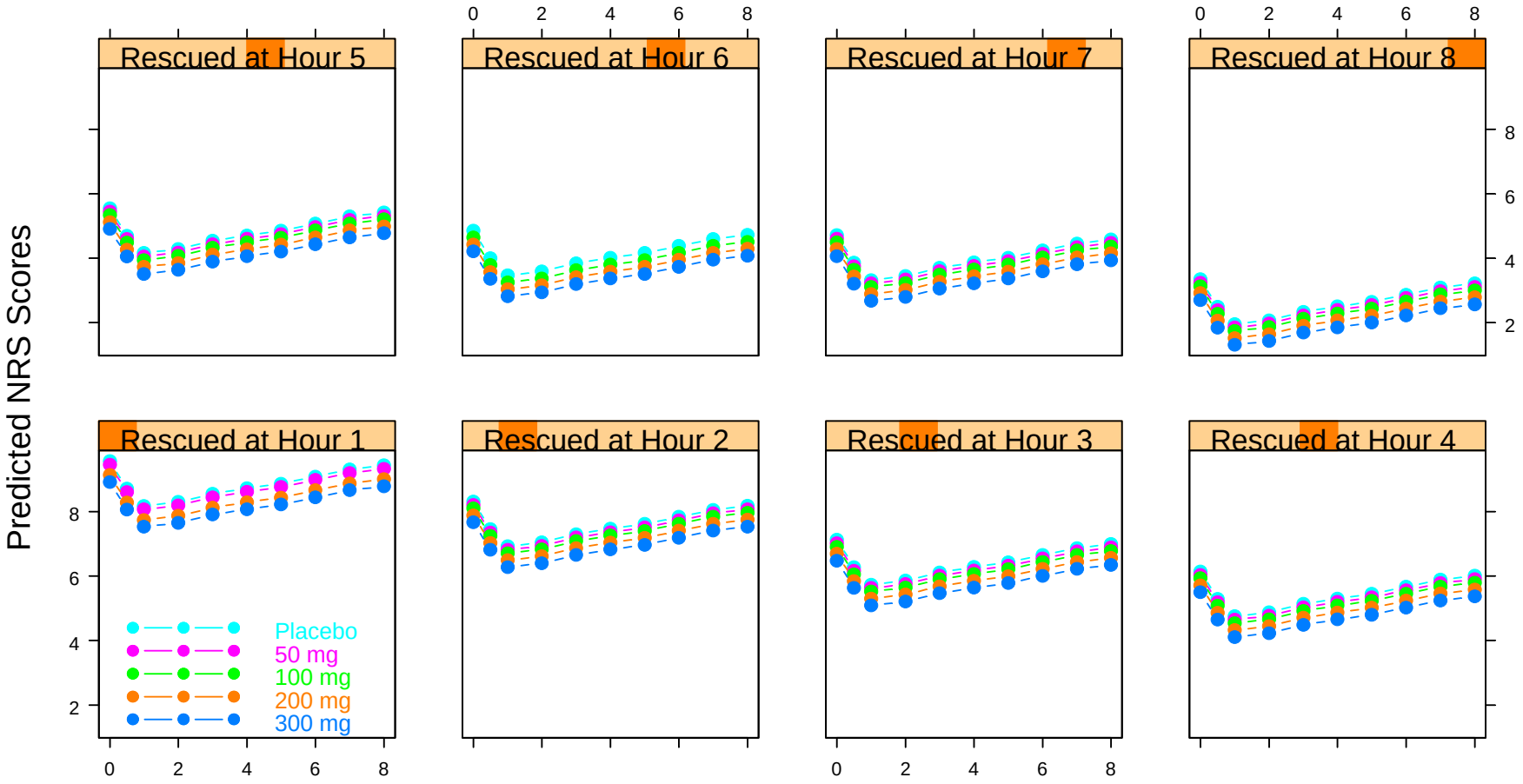

Predicted NRS vs. Time
Model Built with LOCF Imputed Data
With time of rescue
Predicted NRS Scores
2
4
6
8
0
2
4
6
8
Hours on Study


Predicted NRS vs. Time
Model Built with LOCF Imputed Data
Without time of rescue
Predicted NRS Scores
3
4
5
6
7
0
2
4
6
8
Hours on Study

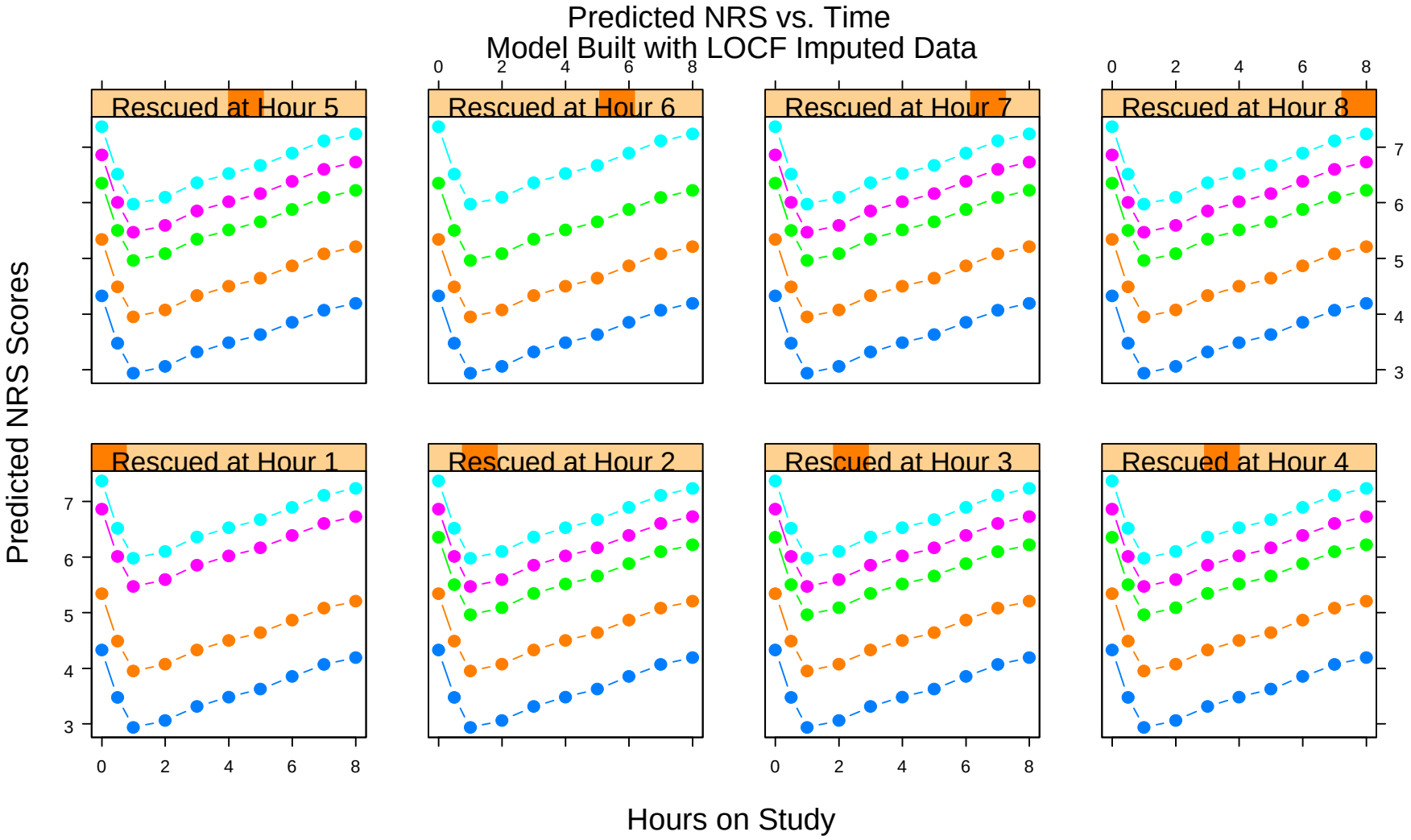

Mean Pain Intensity Over Time by Time of Rescue
A Single-dose Acute Pain Study
All Available Data
All LOCF Data
Mean Numeric Rating Scale
0
2
4
6
8
10
0
2
4
6
8
Hours on Study

Predicted NRS vs. Time
Model Built with LOCF Imputed Data

With time of rescue



Without time of rescue



Estimated PTE

- Using all-available data, PTE is estimated to be 72%.
- Using LOCF imputed data, PTE is estimated to be 78%.

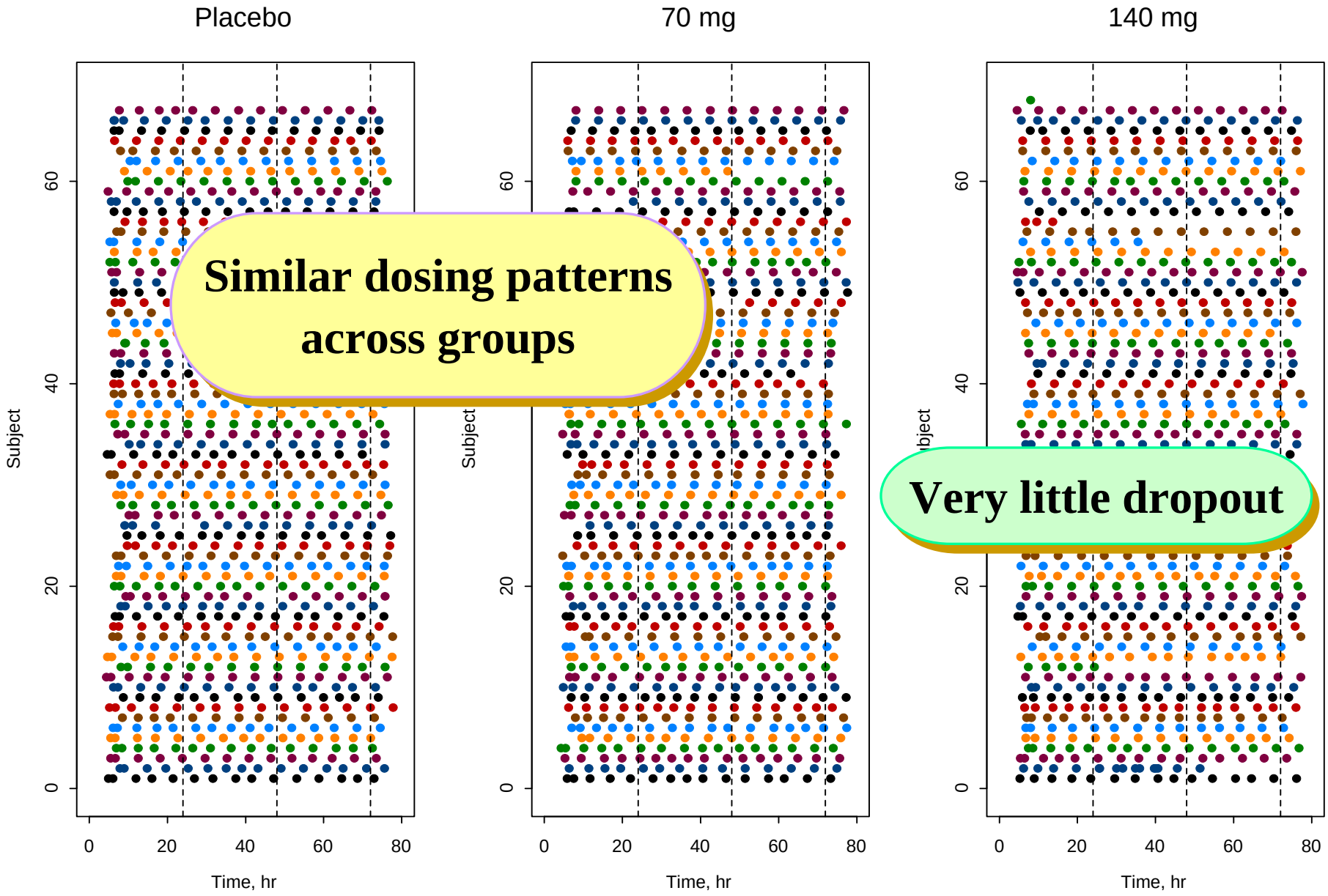
Scenario 2: Rescue Allowed

Compromised Primary Efficacy Variable

Example II

- A repeated-dose acute-pain study of 3-days duration
- Rescue allowed

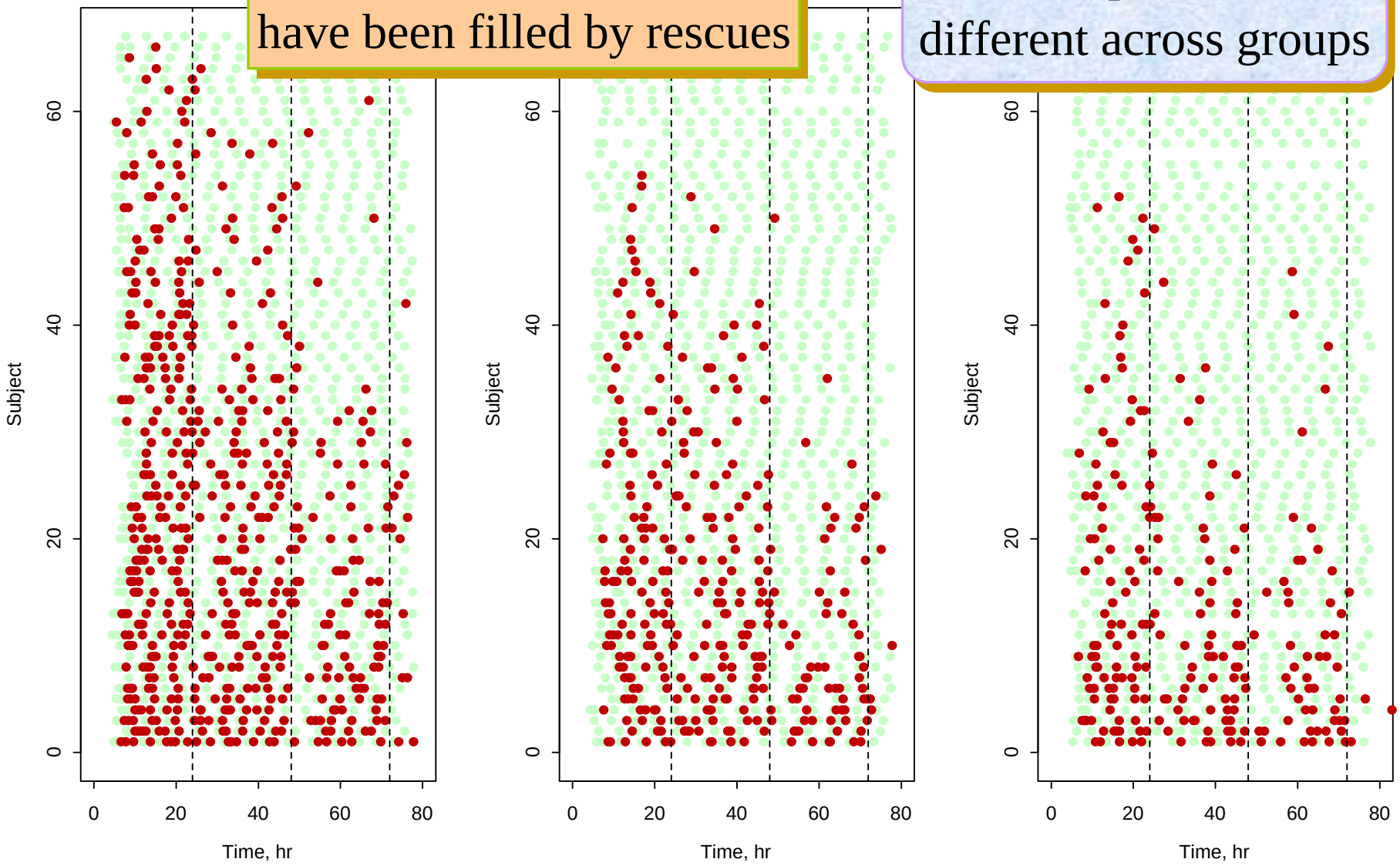
Drug Intake

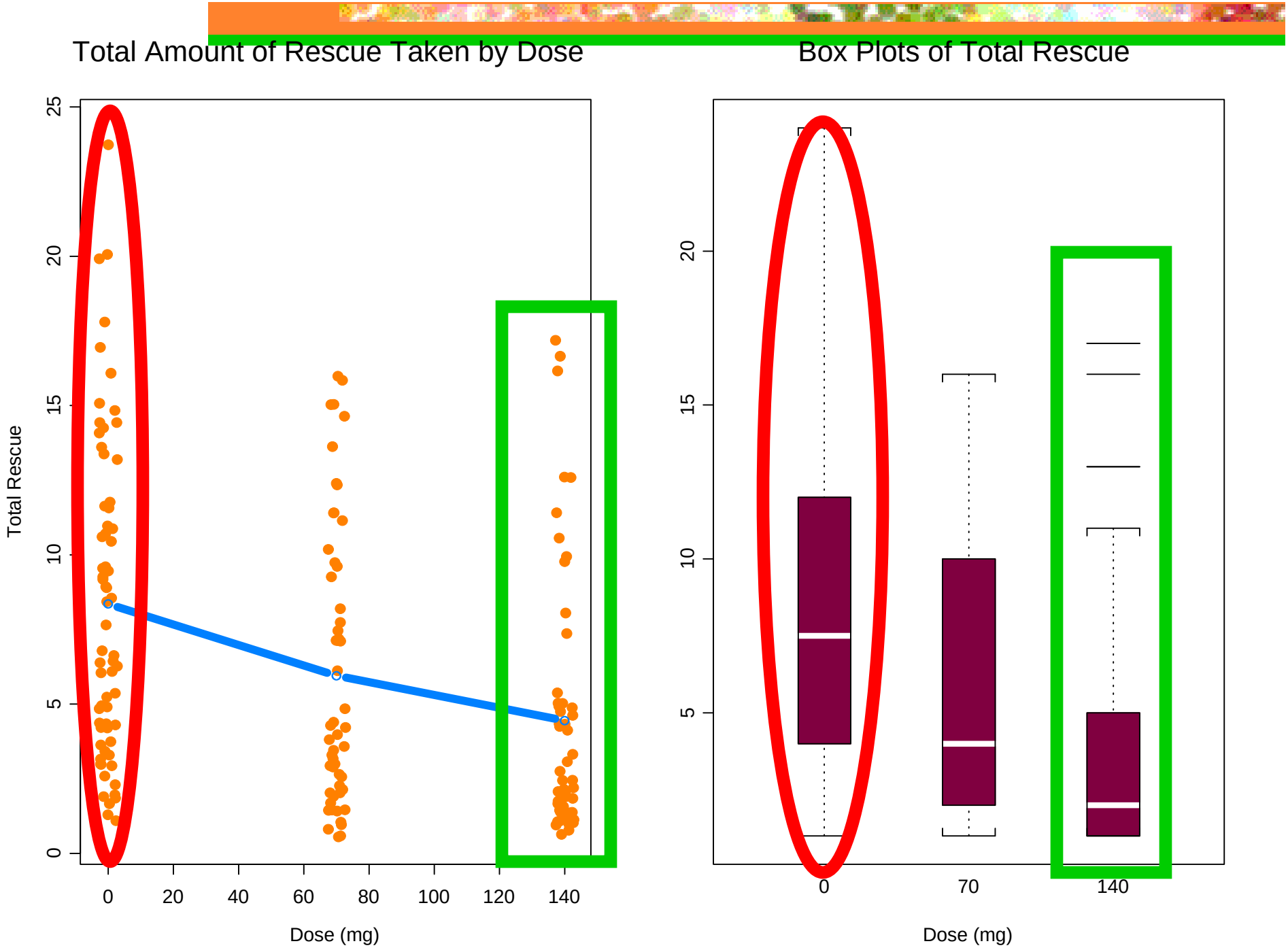

Placebo
70 mg
140 mg
Subject
Time, hr
0
20
40
60
80
Similar dosing patterns across groups
Very little dropout

Rescue Intake

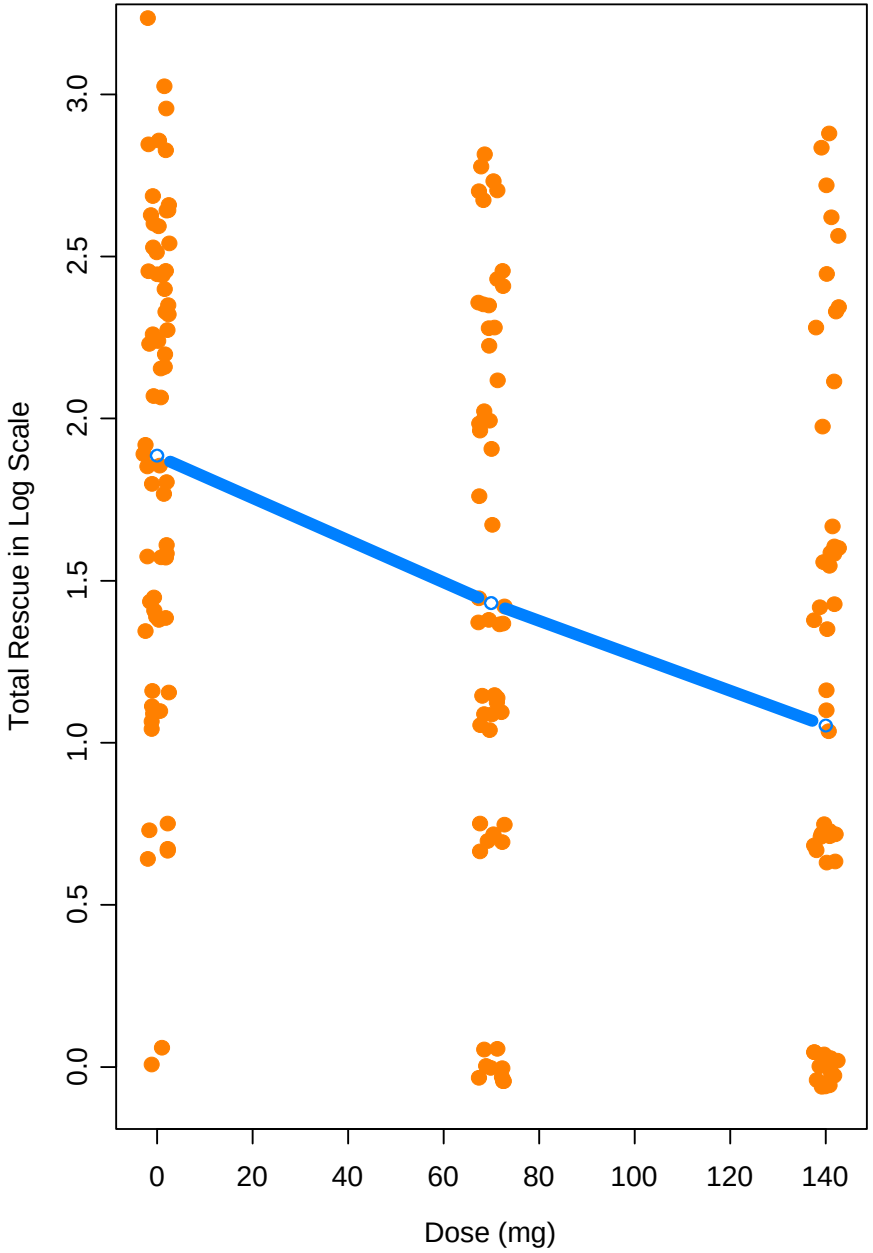
Many gaps in dosing have been filled by rescues

Rescue patterns are different across groups

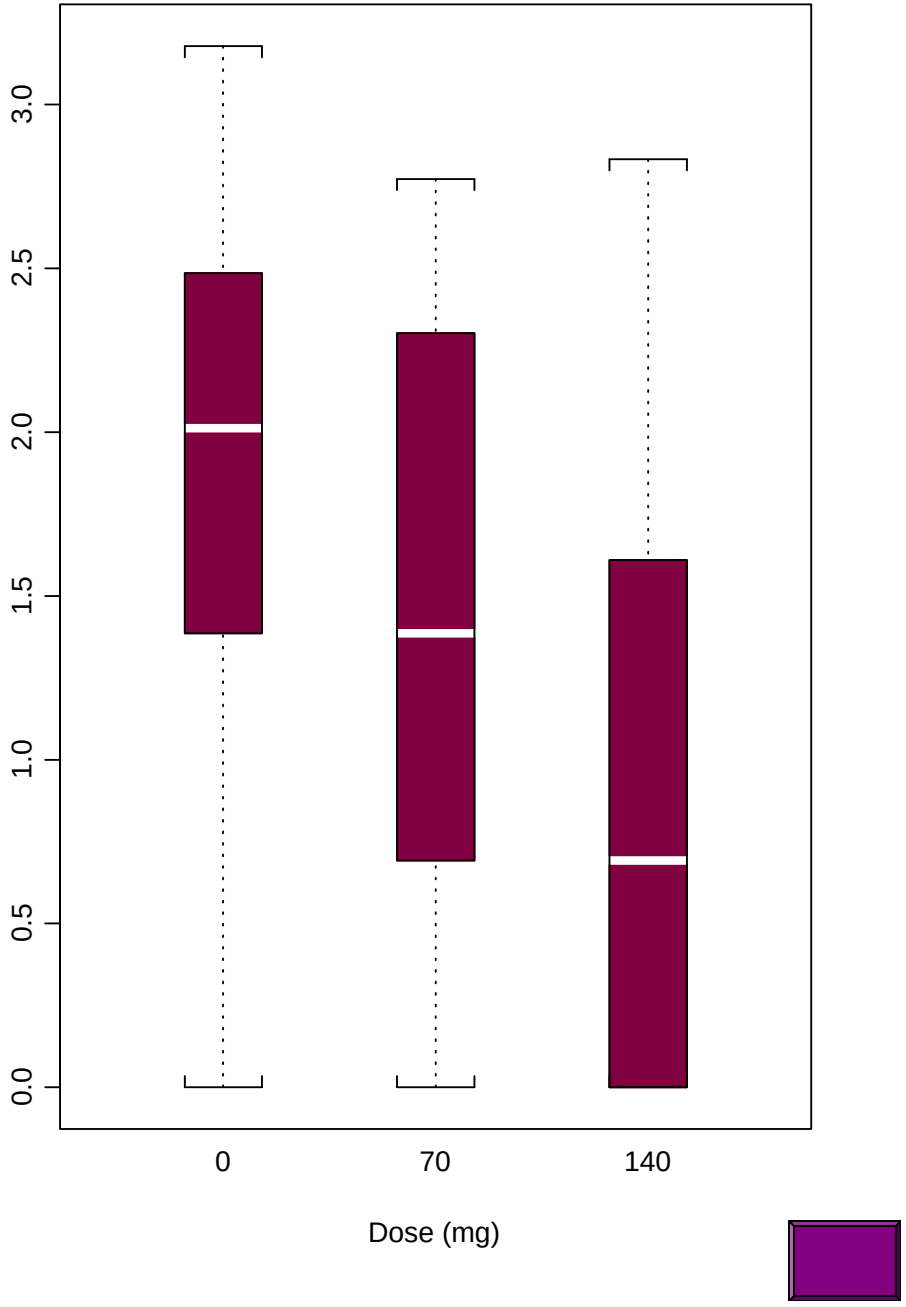


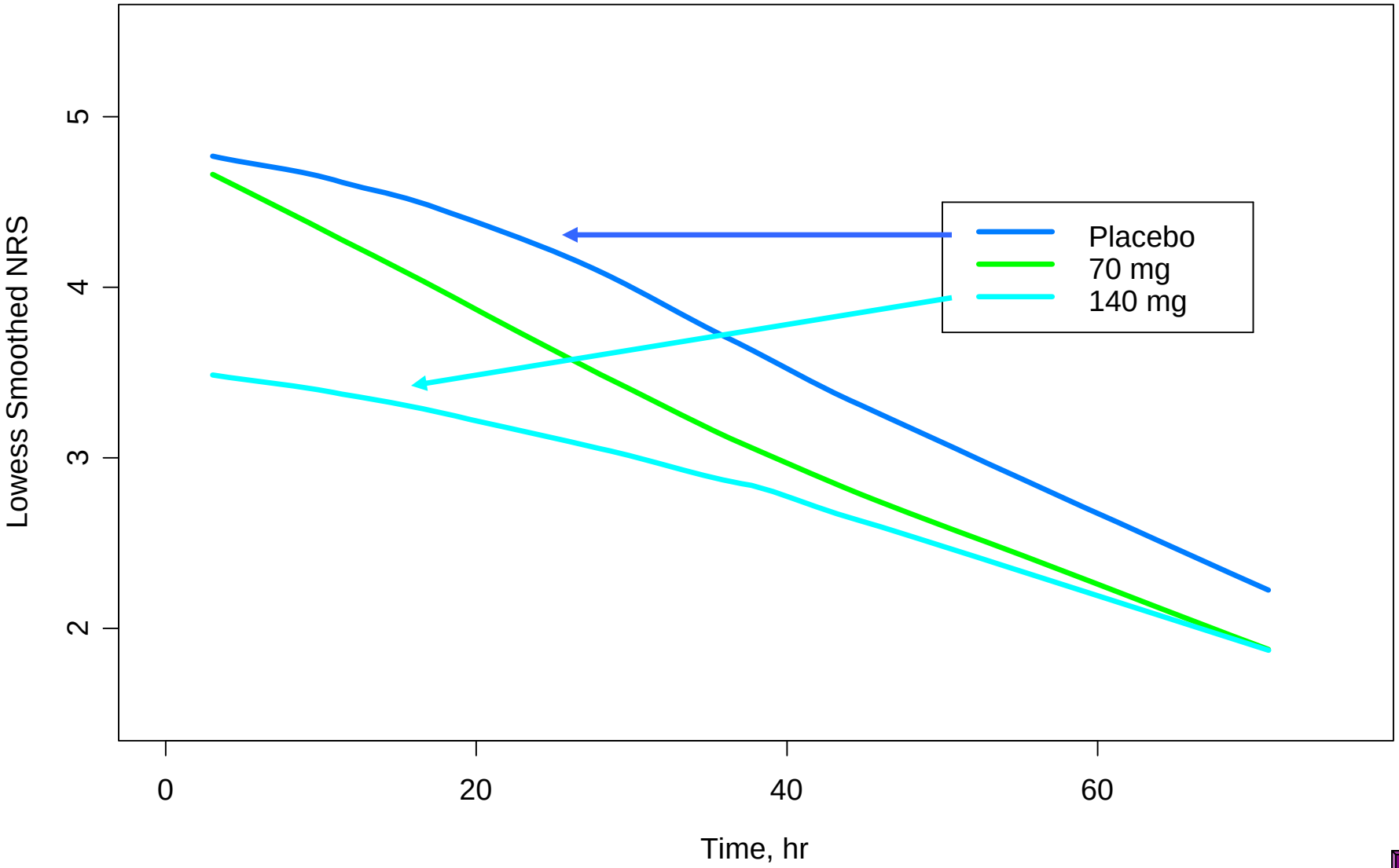

Total Amount of Rescue Taken by Dose
Total Rescue
0
5
10
15
20
25
0
20
40
60
80
100
120
140
Dose (mg)
Box Plots of Total Rescue
5
10
15
20
0
70
140
Dose (mg)

Total Amount of Rescue Taken in Log Scale

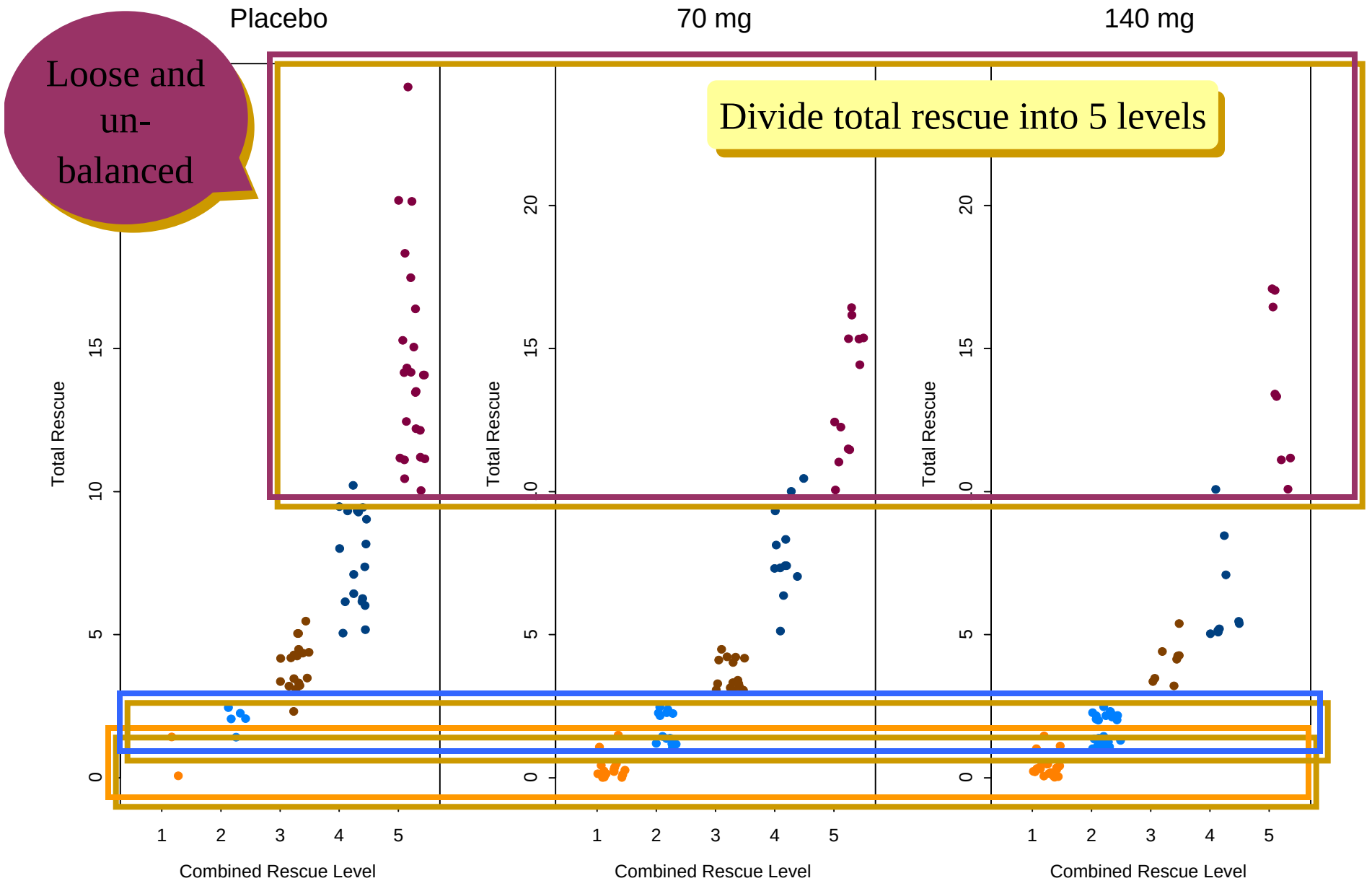


Box Plots of Total Rescue in Log Scale

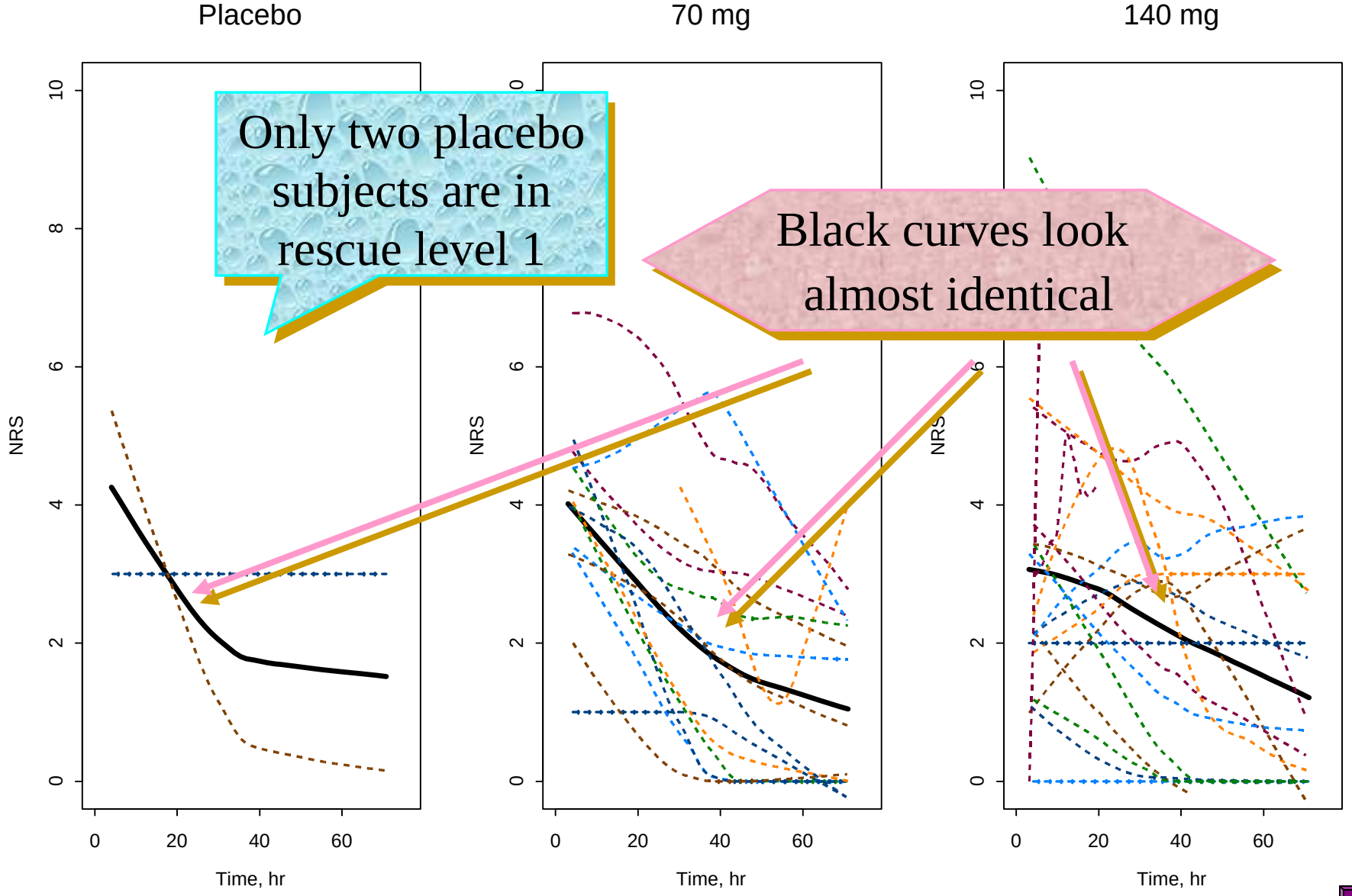


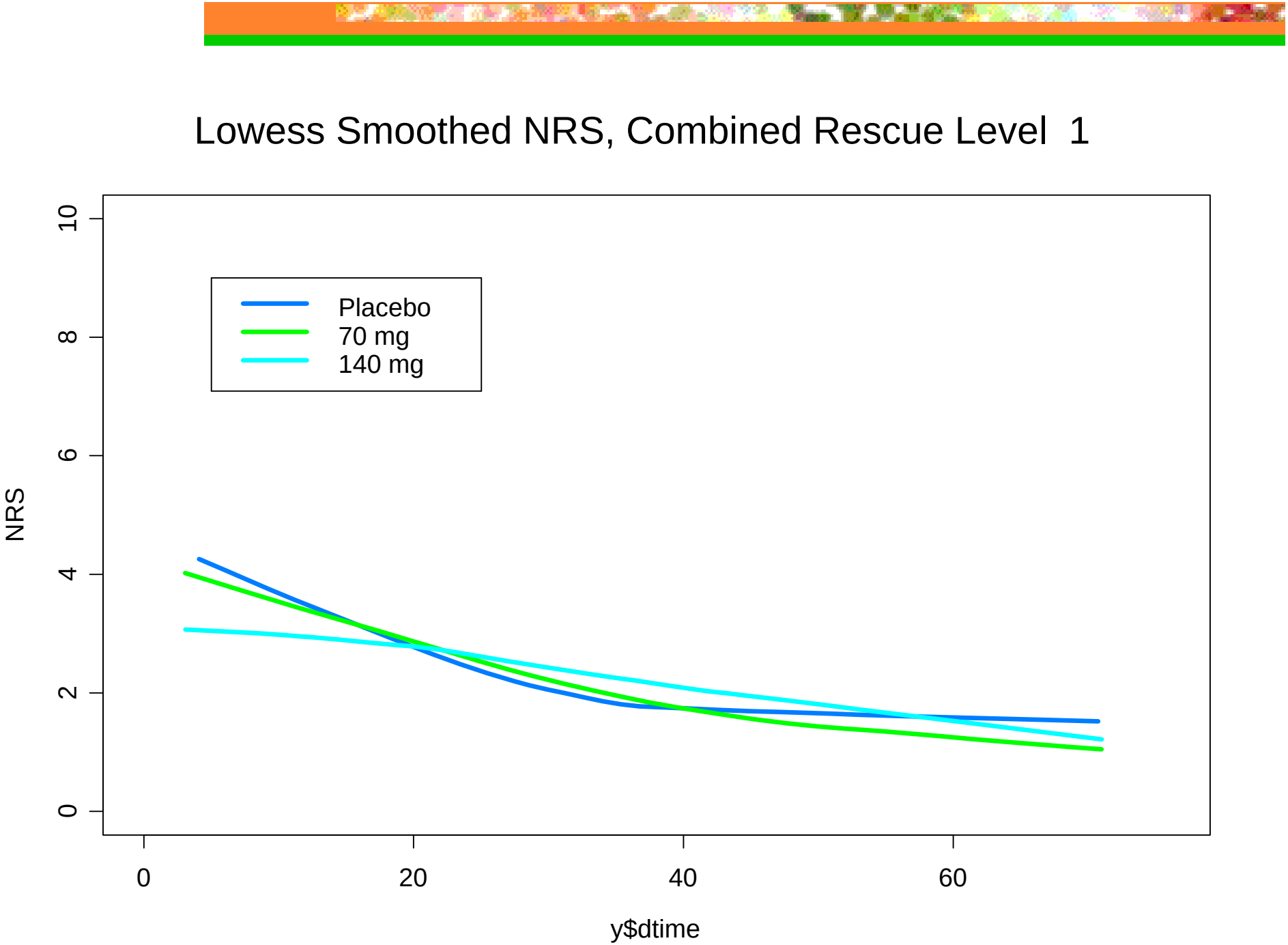

NRS Profile over Time
Lowess Smoothed NRS
2
3
4
5
0
20
40
60
Time, hr
Placebo
70 mg
140 mg

Distribution of Total Rescue

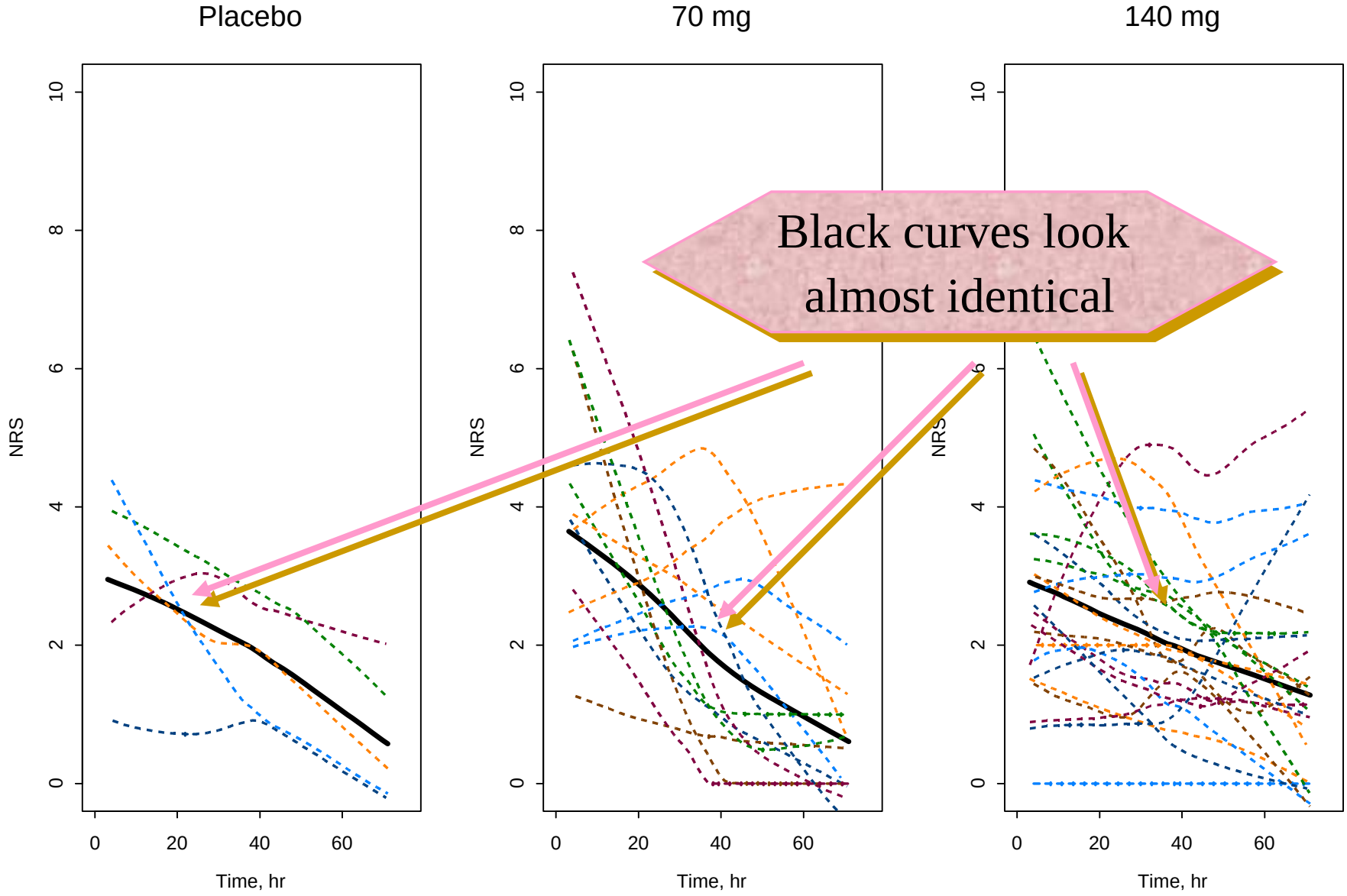


Pain Profile by Rescue Level
Combined Rescue Level 1

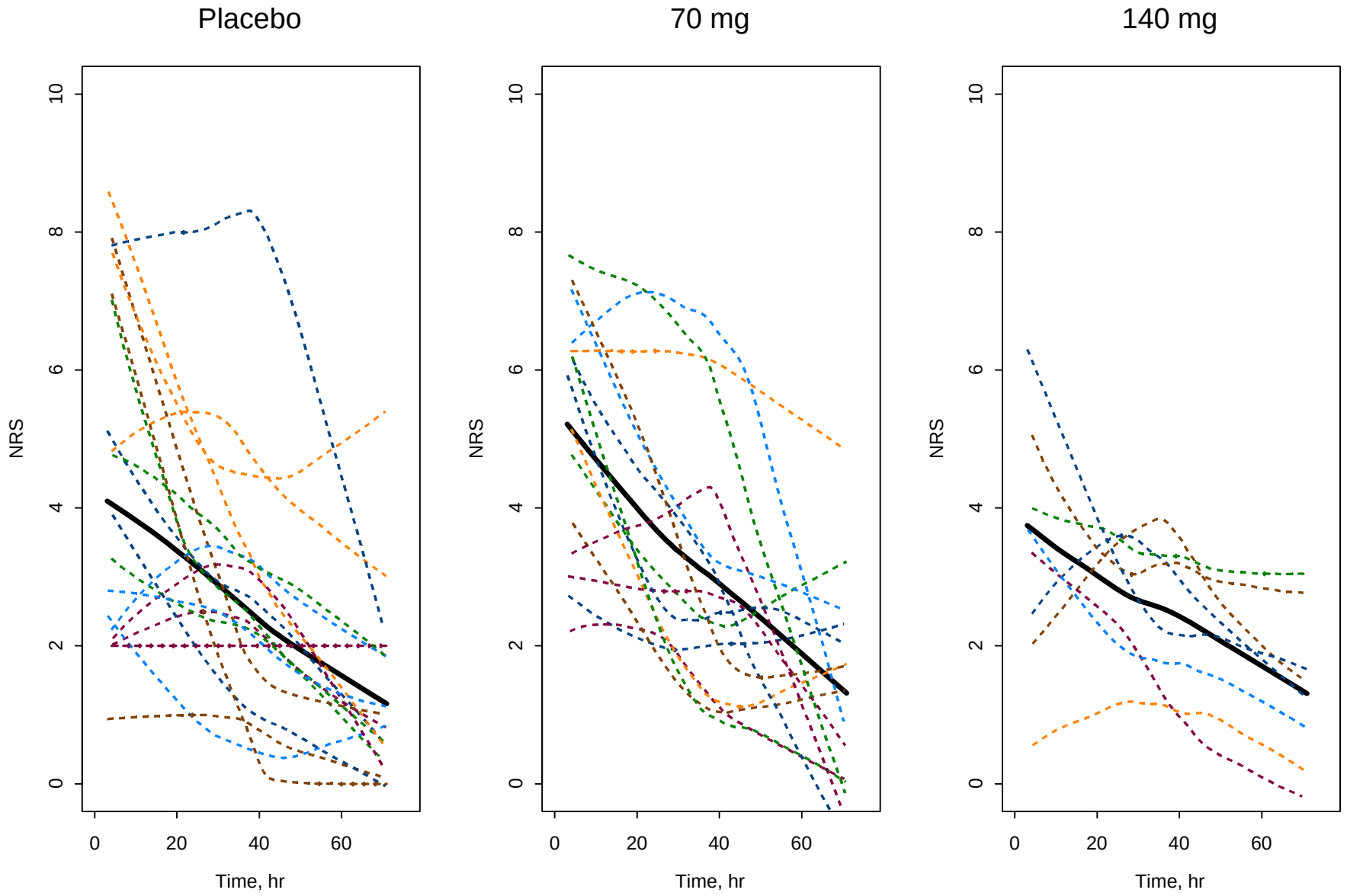



Lowess Smoothed NRS, Combined Rescue Level 1
Placebo
70 mg
140 mg
NRS
0
2
4
6
8
10
0
20
40
60
y$dtime

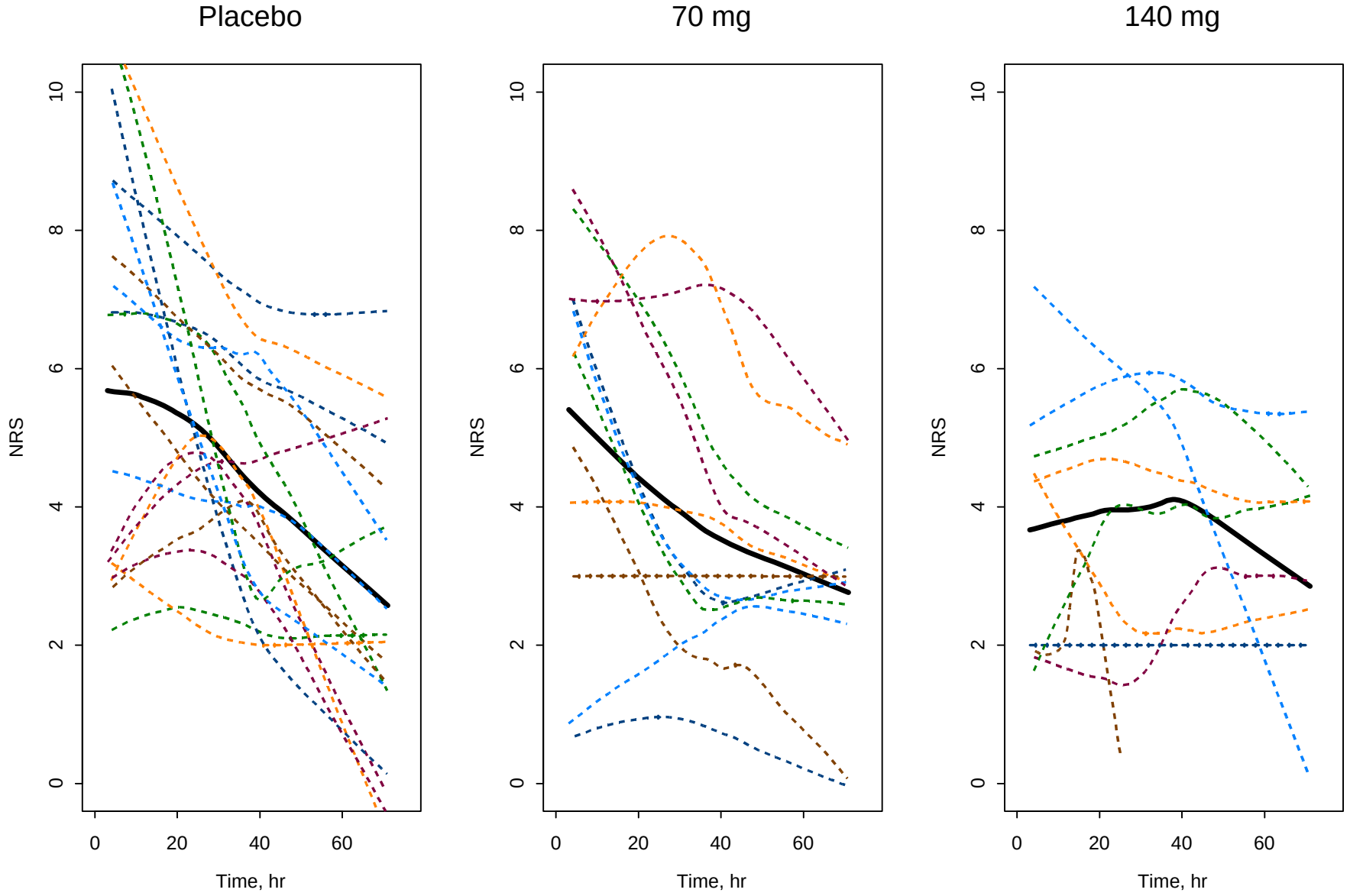
Pain Profile by Rescue Level
Combined Rescue Level 2



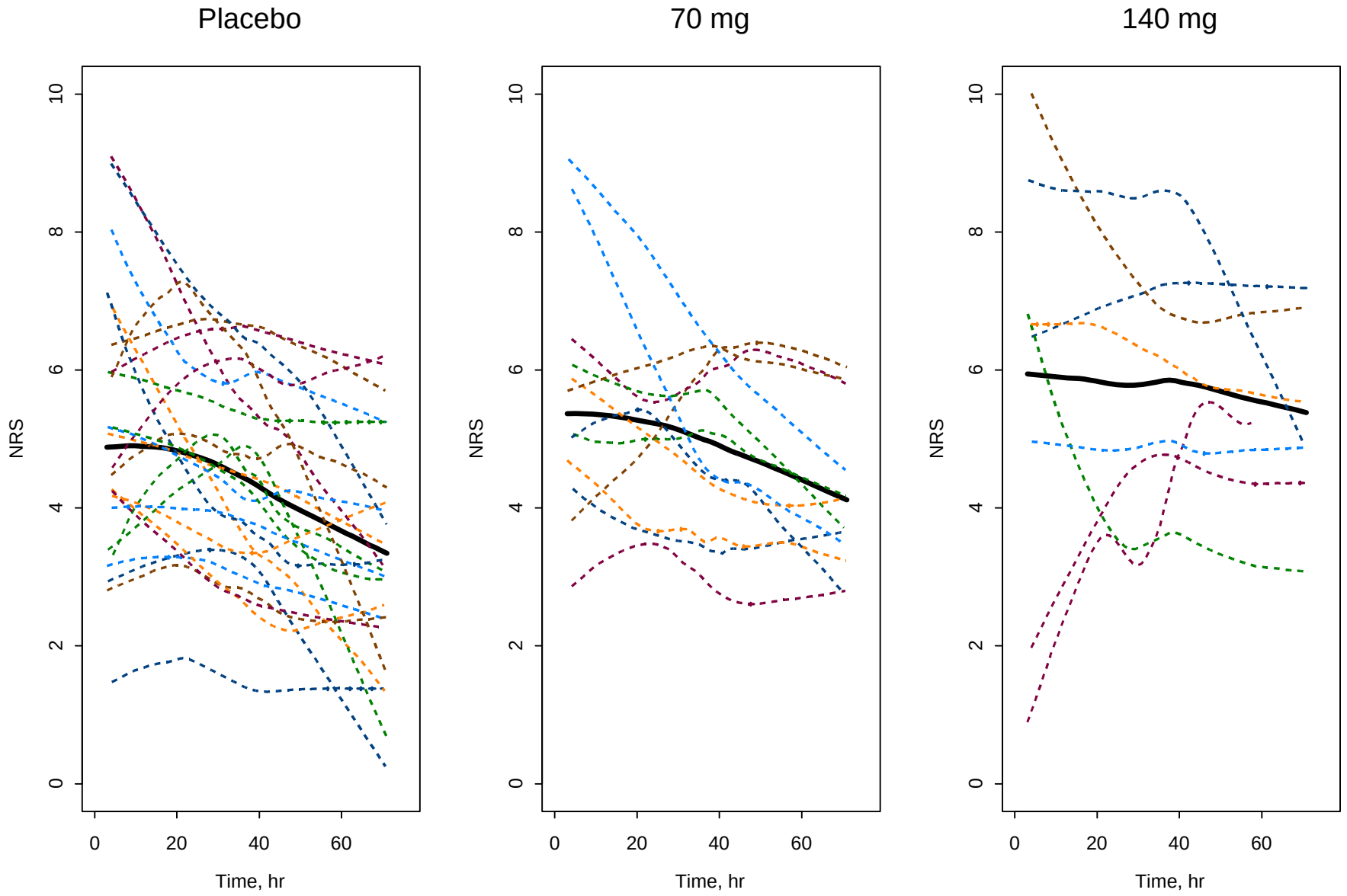
Pain Profile by Rescue Level
Combined Rescue Level 3

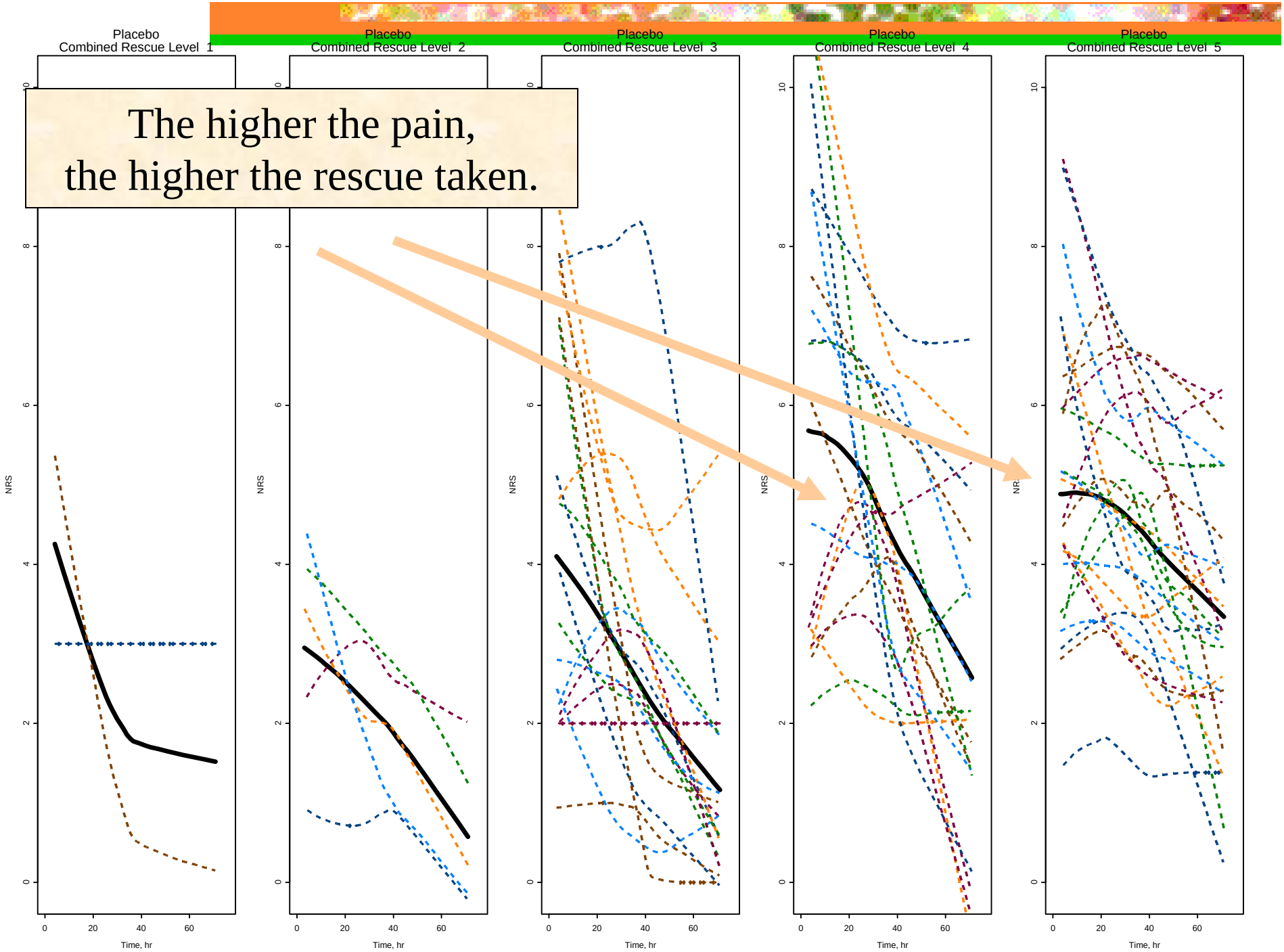


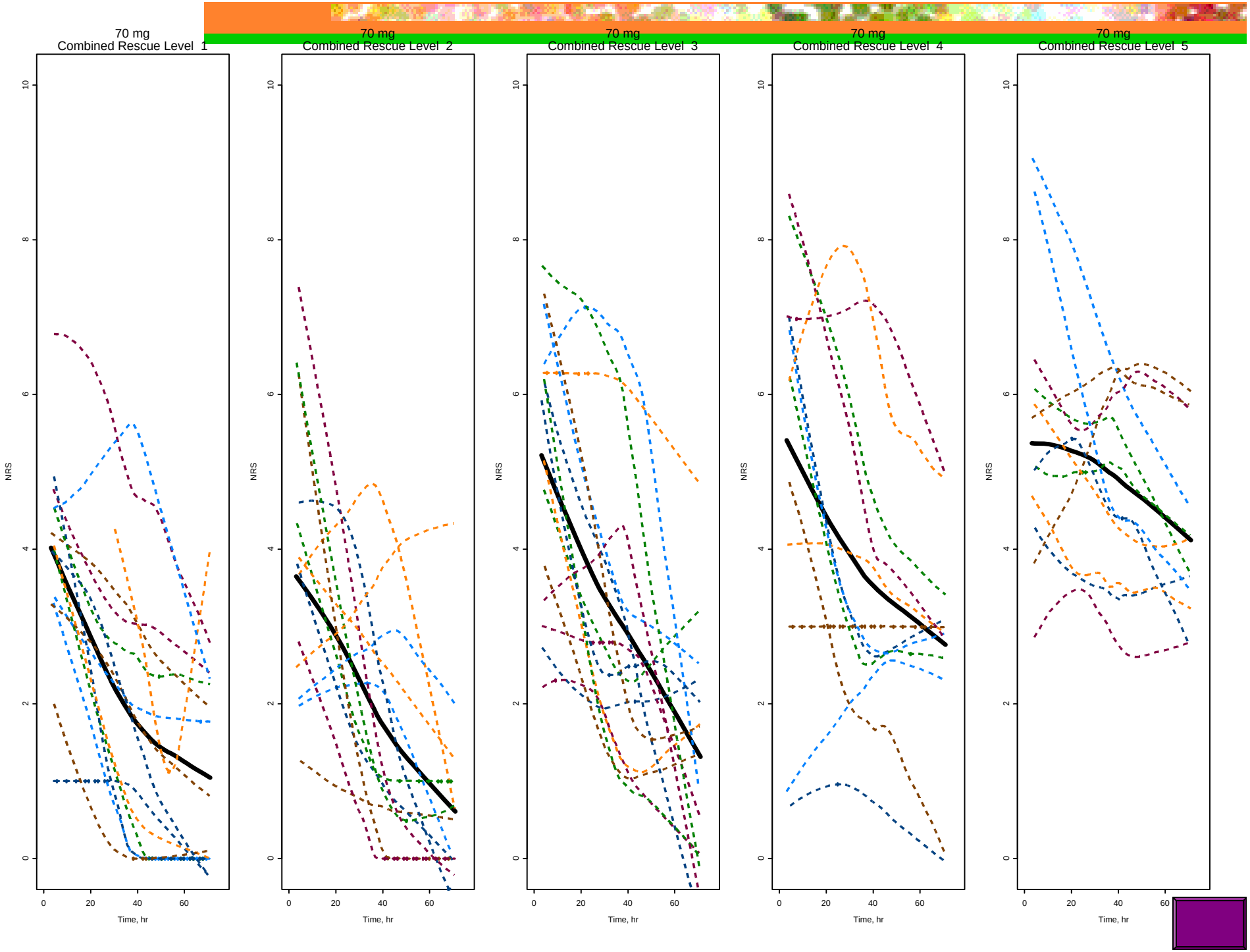
Pain Profile by Rescue Level
Combined Rescue Level 4

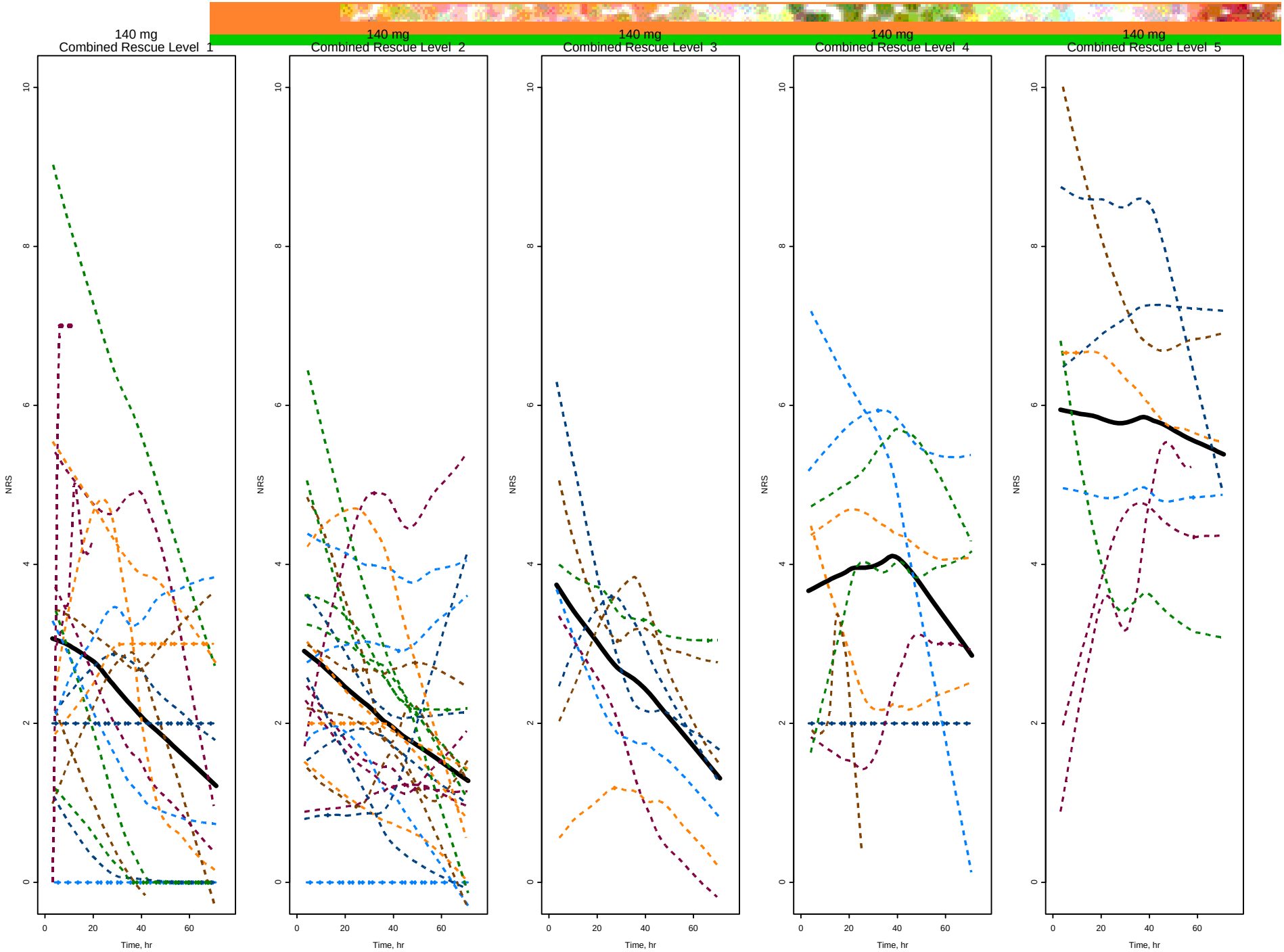


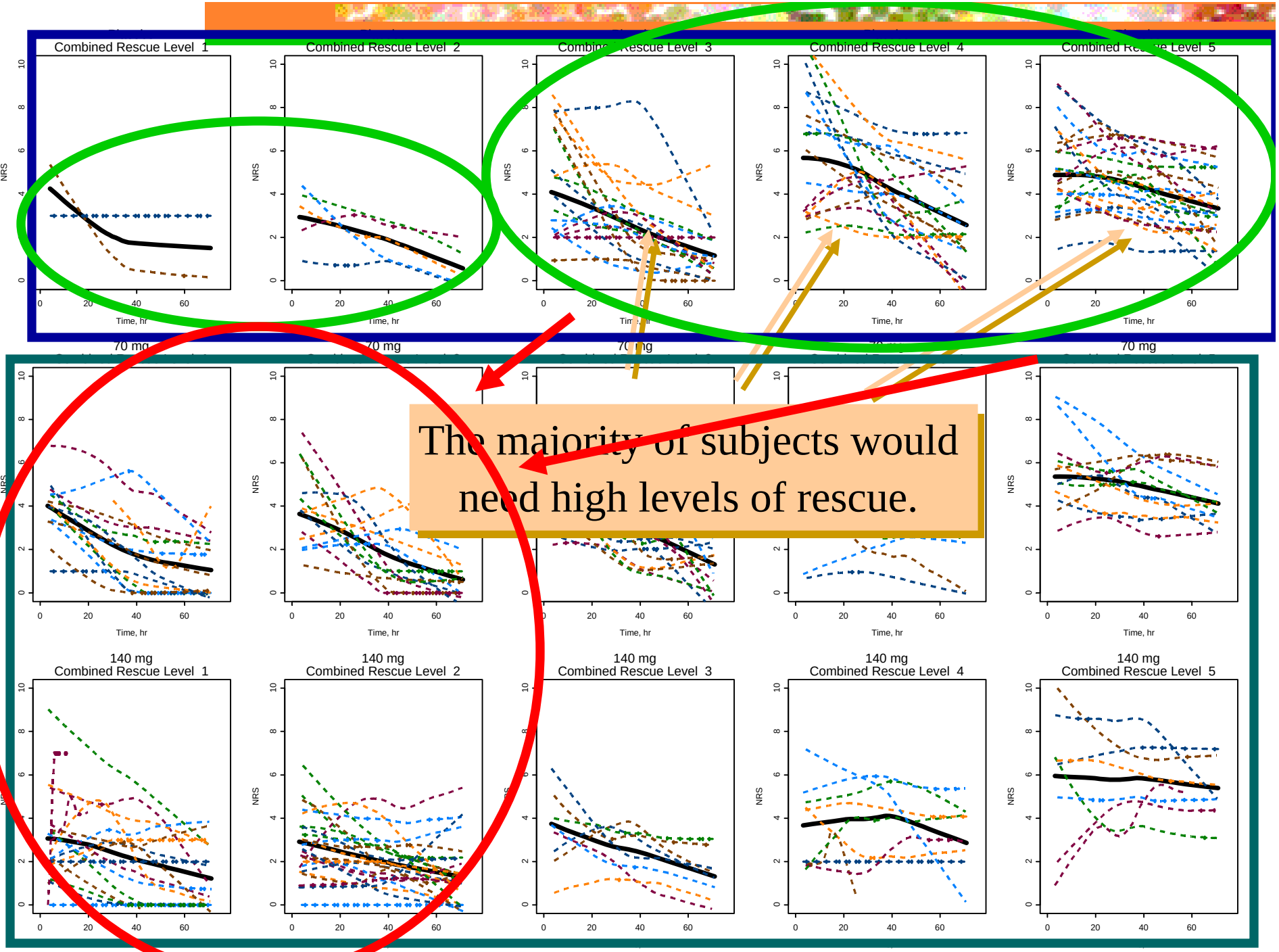
Pain Profile by Rescue Level
Combined Rescue Level 5



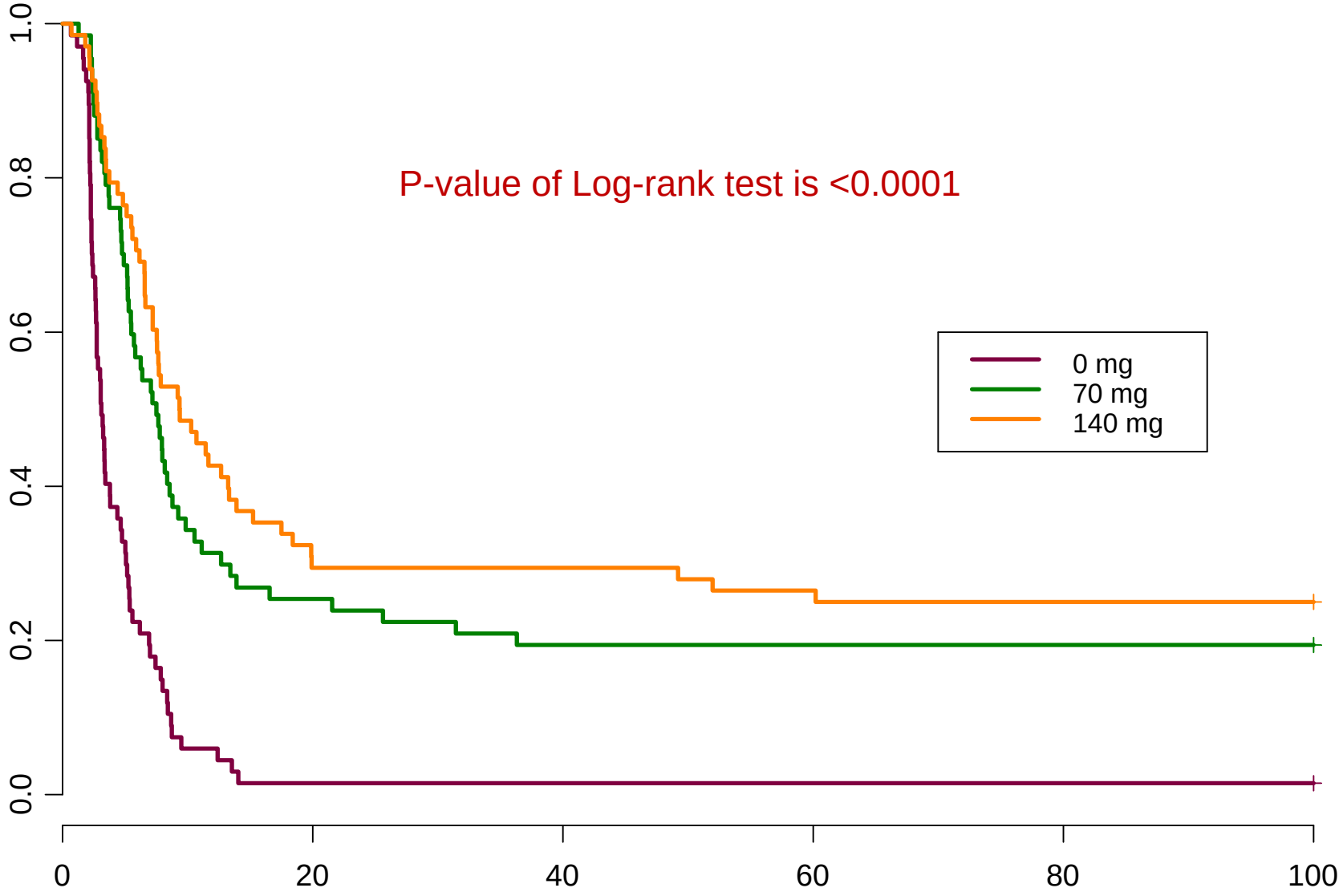

Placebo
Combined Rescue Level 1
Placebo
Combined Rescue Level 2
Placebo
Combined Rescue Level 3
Placebo
Combined Rescue Level 4
Placebo
Combined Rescue Level 5
The higher the pain,
the higher the rescue taken.
NRS
Time, hr
0
2
4
6
8
10
0
20
40
60

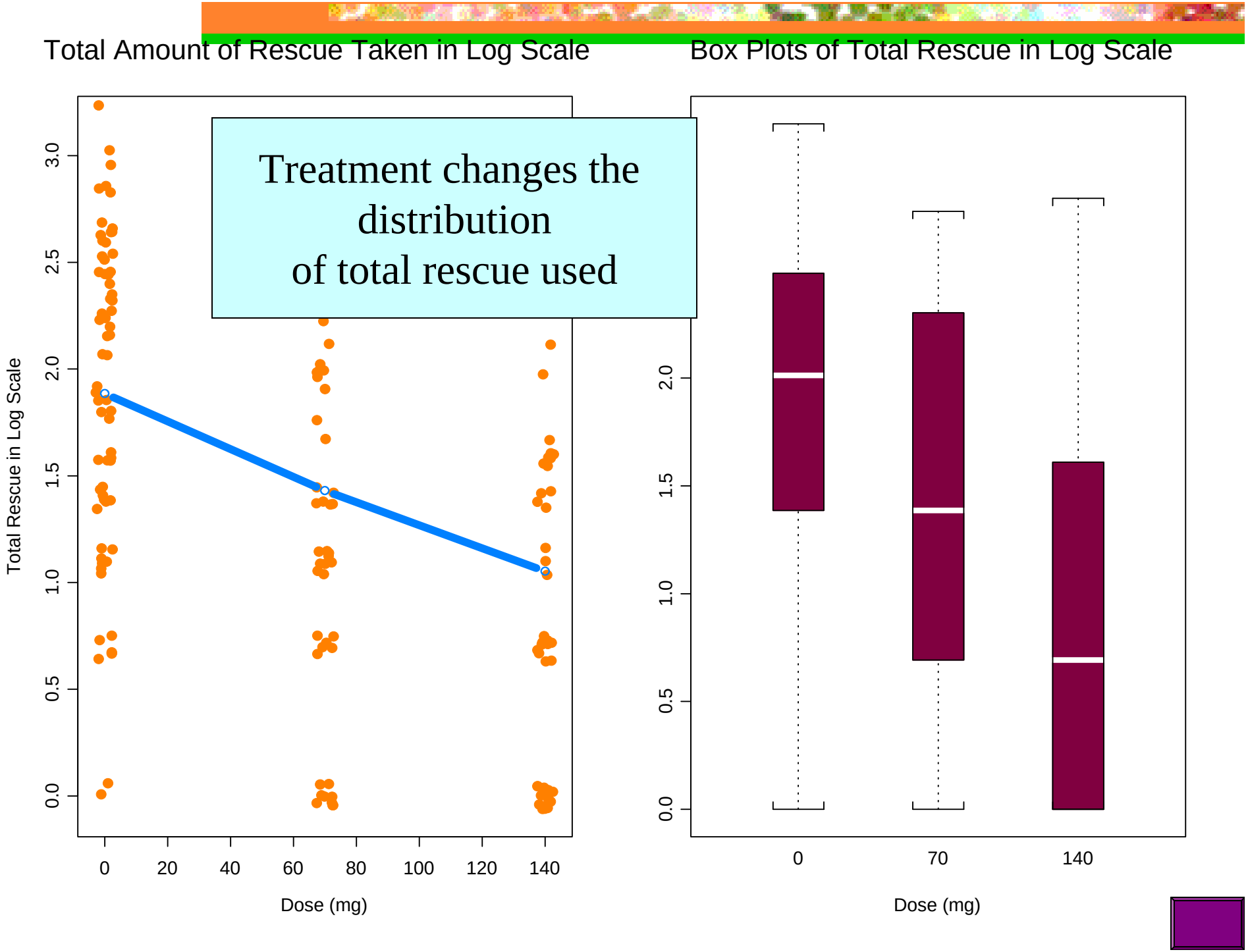

70 mg
Combined Rescue Level 1
70 mg
Combined Rescue Level 2
70 mg
Combined Rescue Level 3
70 mg
Combined Rescue Level 4
70 mg
Combined Rescue Level 5
NRS
Time, hr
0
2
4
6
8
10
0
20
40
60

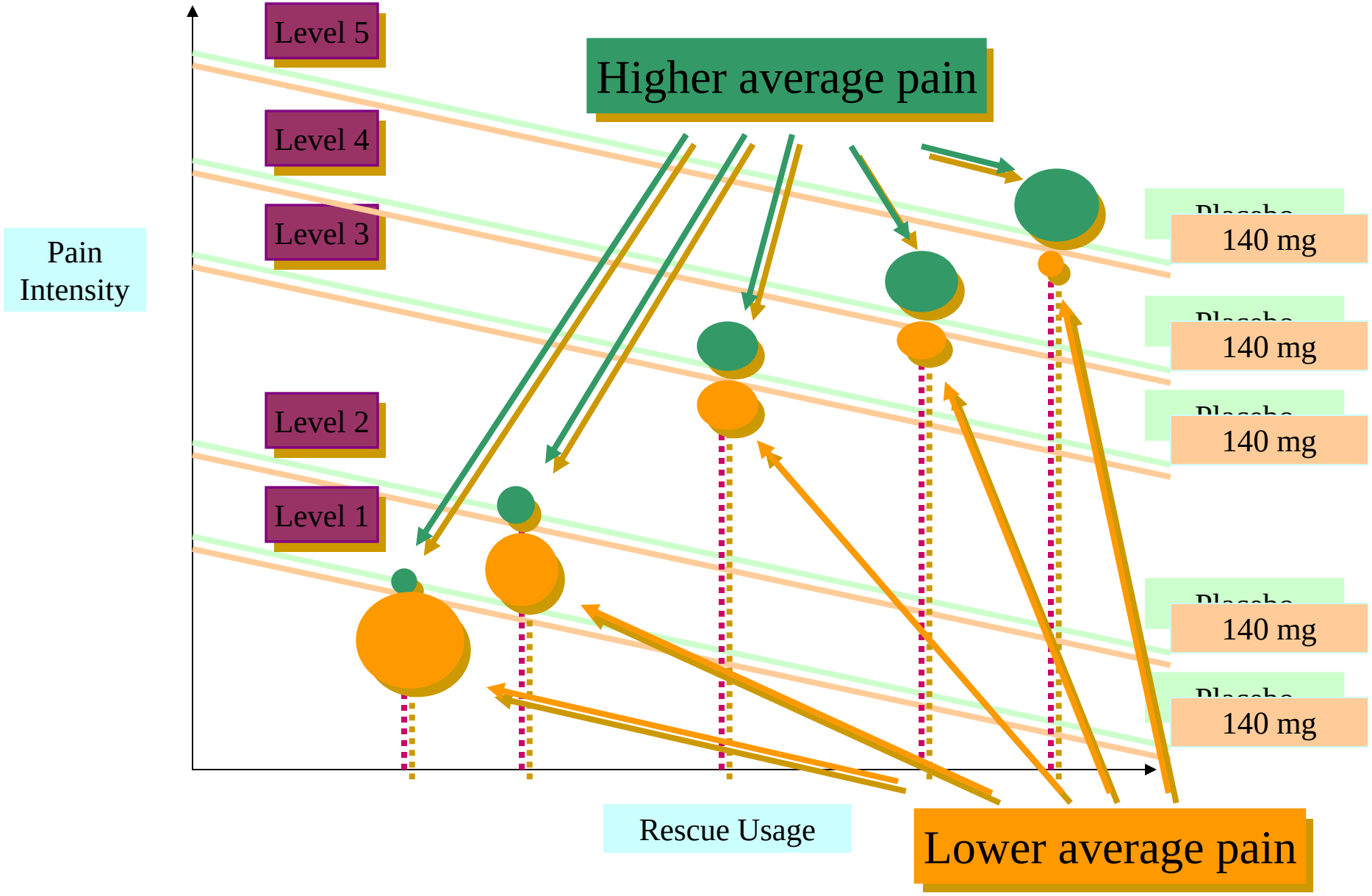

140 mg
Combined Rescue Level 1
140 mg
Combined Rescue Level 2
140 mg
Combined Rescue Level 3
140 mg
Combined Rescue Level 4
140 mg
Combined Rescue Level 5
NRS
Time, hr
0
2
4
6
8
10
0
20
40
60

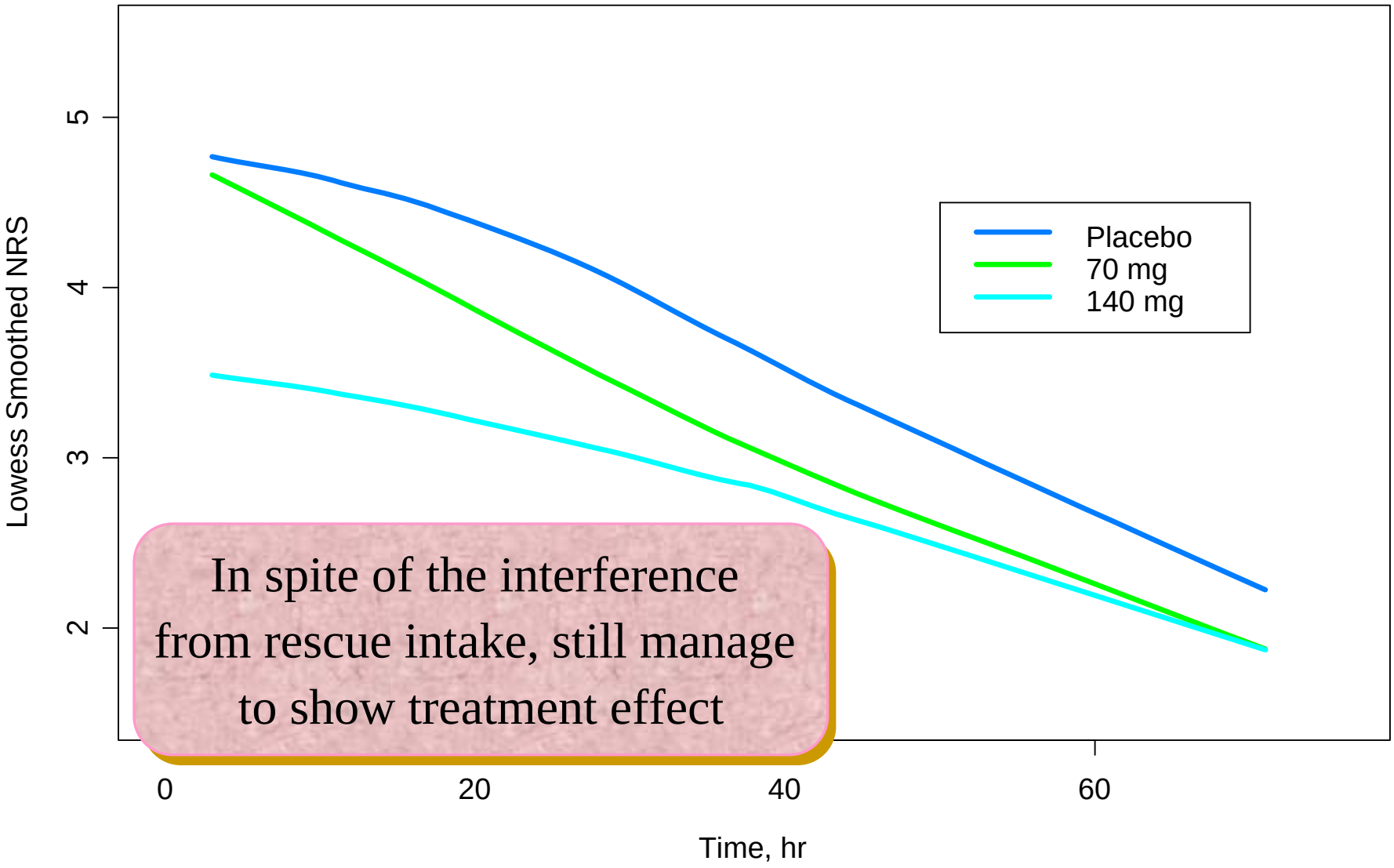

Combined Rescue Level 1
Combined Rescue Level 2
Combined Rescue Level 3
Combined Rescue Level 4
Combined Rescue Level 5
NRS
Time, hr
70 mg
140 mg
The majority of subjects would need high levels of rescue.

Kaplan-Meier Survival Curves for Time to Rescue
A Repeated-dose Acute Pain Study




Total Amount of Rescue Taken in Log Scale
Box Plots of Total Rescue in Log Scale
Treatment changes the distribution of total rescue used
Total Rescue in Log Scale
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
20
40
60
80
100
120
140
Dose (mg)
0
70
140
Dose (mg)


Level 5
Level 4
Level 3
Level 2
Level 1
Higher average pain
Pain Intensity
Placebo
140 mg
Placebo
140 mg
Placebo
140 mg
Placebo
140 mg
Placebo
140 mg
Rescue Usage
Lower average pain


NRS Profile over Time
Lowess Smoothed NRS
5
4
3
2
Placebo
70 mg
140 mg
In spite of the interference from rescue intake, still manage to show treatment effect
0
20
40
60
Time, hr

What is required to show the total rescue used is a surrogate?

$P (T(t) \mid X, S) = P (T(t) \mid S)$

at all time points of t

$P (T(t)|X) \neq P (T(t))$ at all time points

$P (T(t)|S) \neq P (T(t))$ at some time points

$P (S|X) \neq P (S)$

What do we expect to see in models?

(1) Model P (T(t) | X, S)

at all time points of t

Coefficient of X should be small.

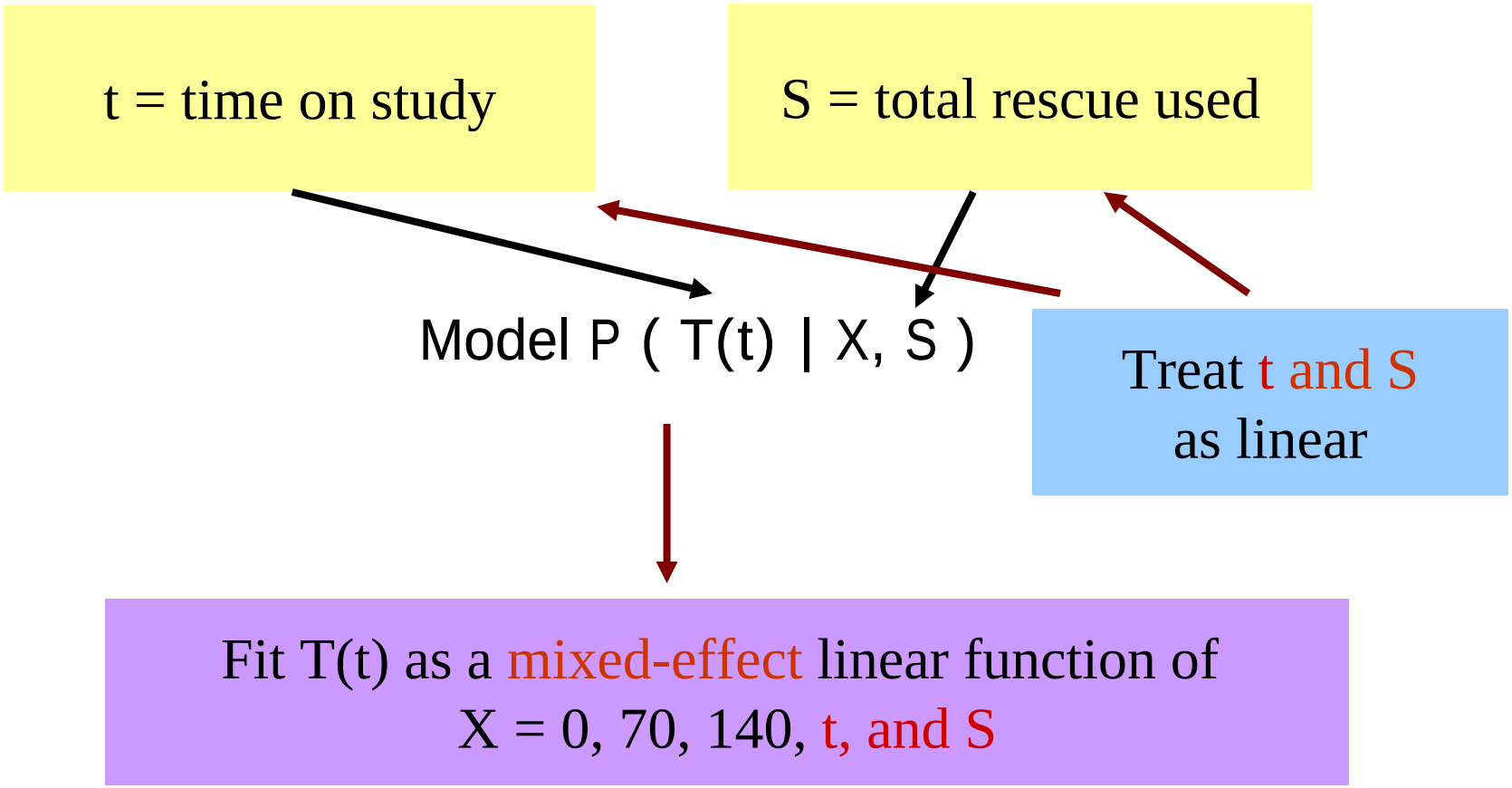
(2) Model P (T(t)|X) at all time points

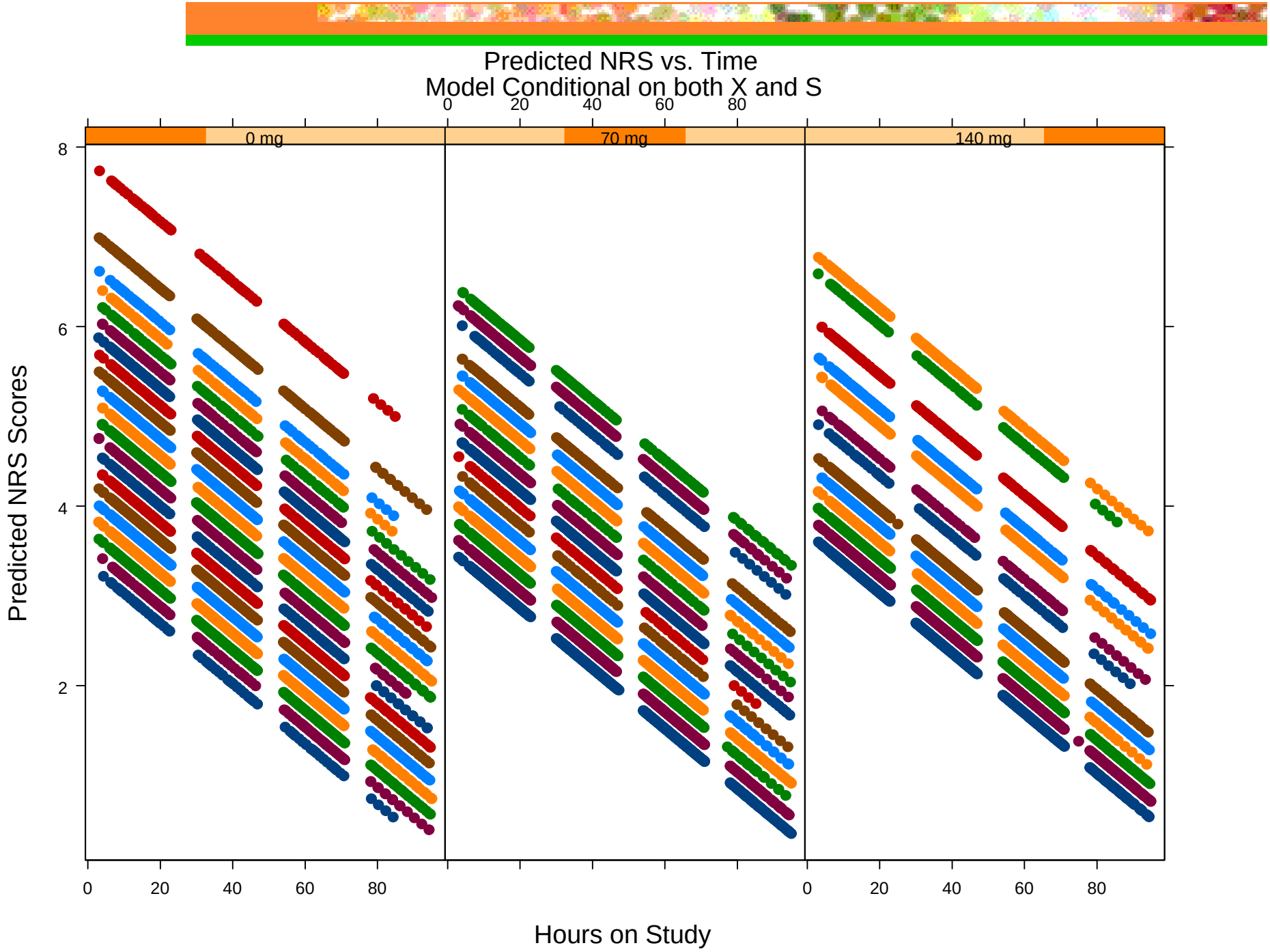
(3) Model P (T(t)|S)

(4) Model P (S|X)

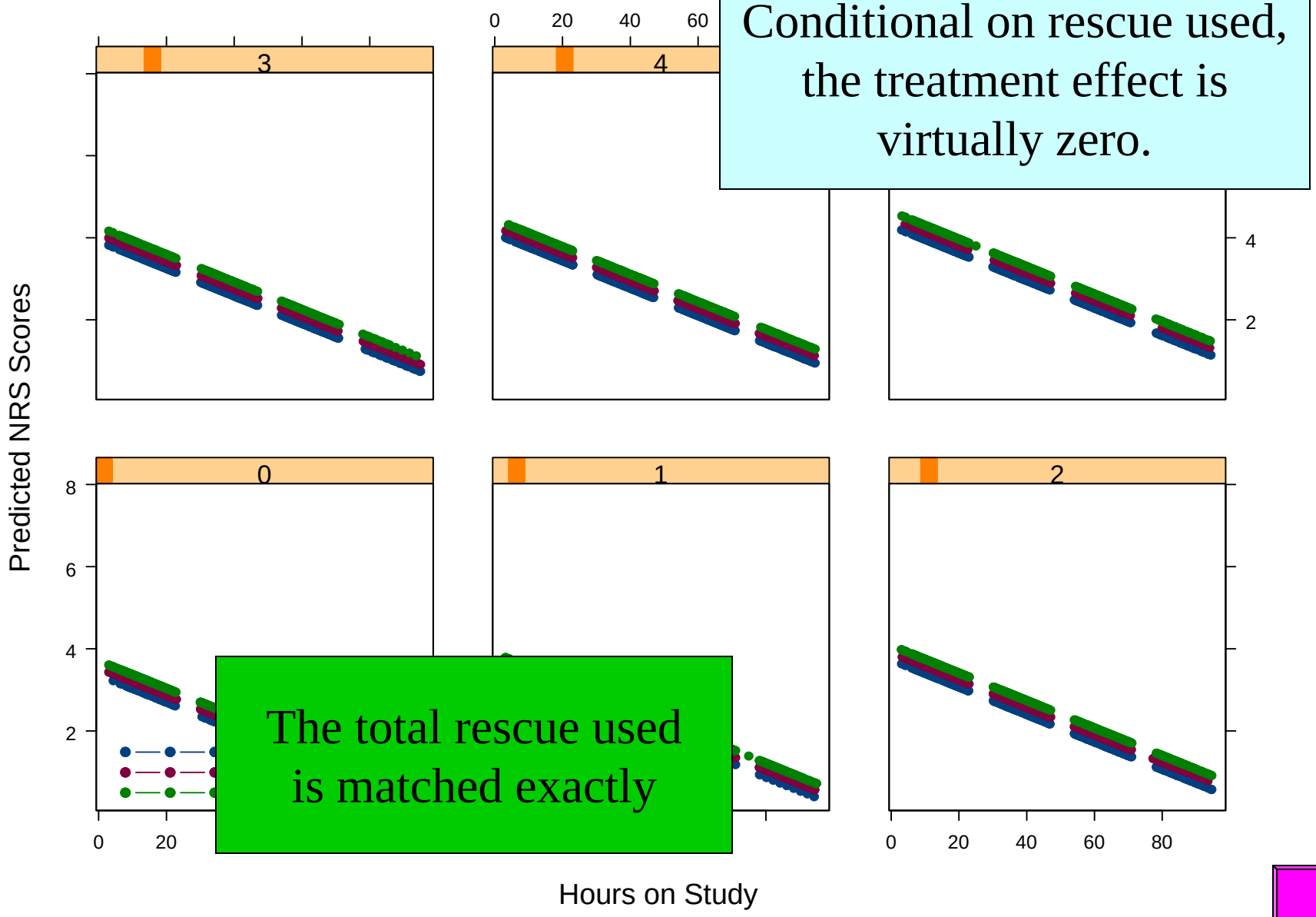
Coefficient of X should be big.

The First Model




Predicted NRS vs. Time
Model Conditional on both X and S
0 mg
70 mg
140 mg
Predicted NRS Scores
Hours on Study
0
20
40
60
80
2
4
6
8

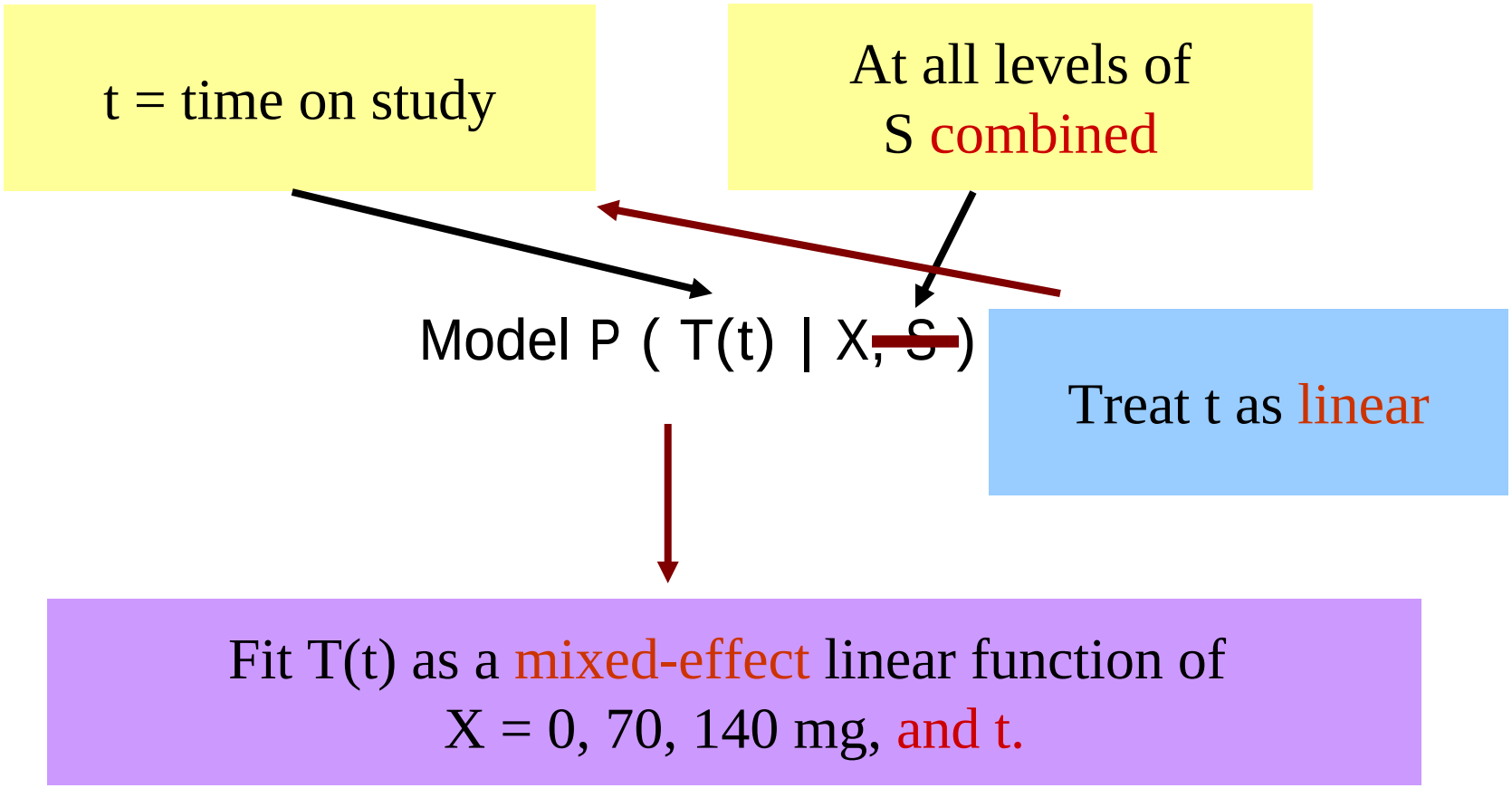
Predicted NRS vs. Time, Model Conditional on both X and S
Stratified by the Total Tablets of Rescue Taken

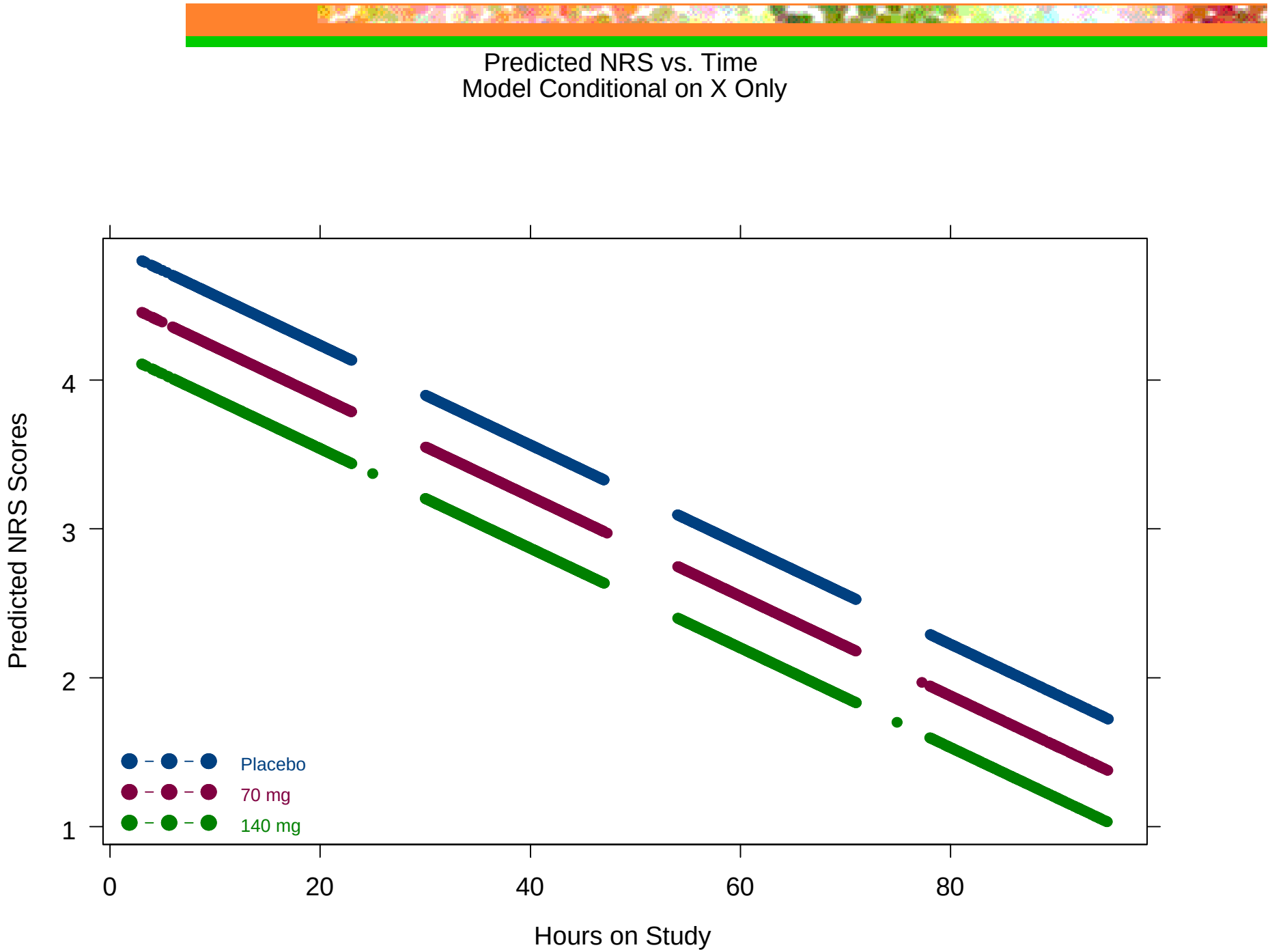


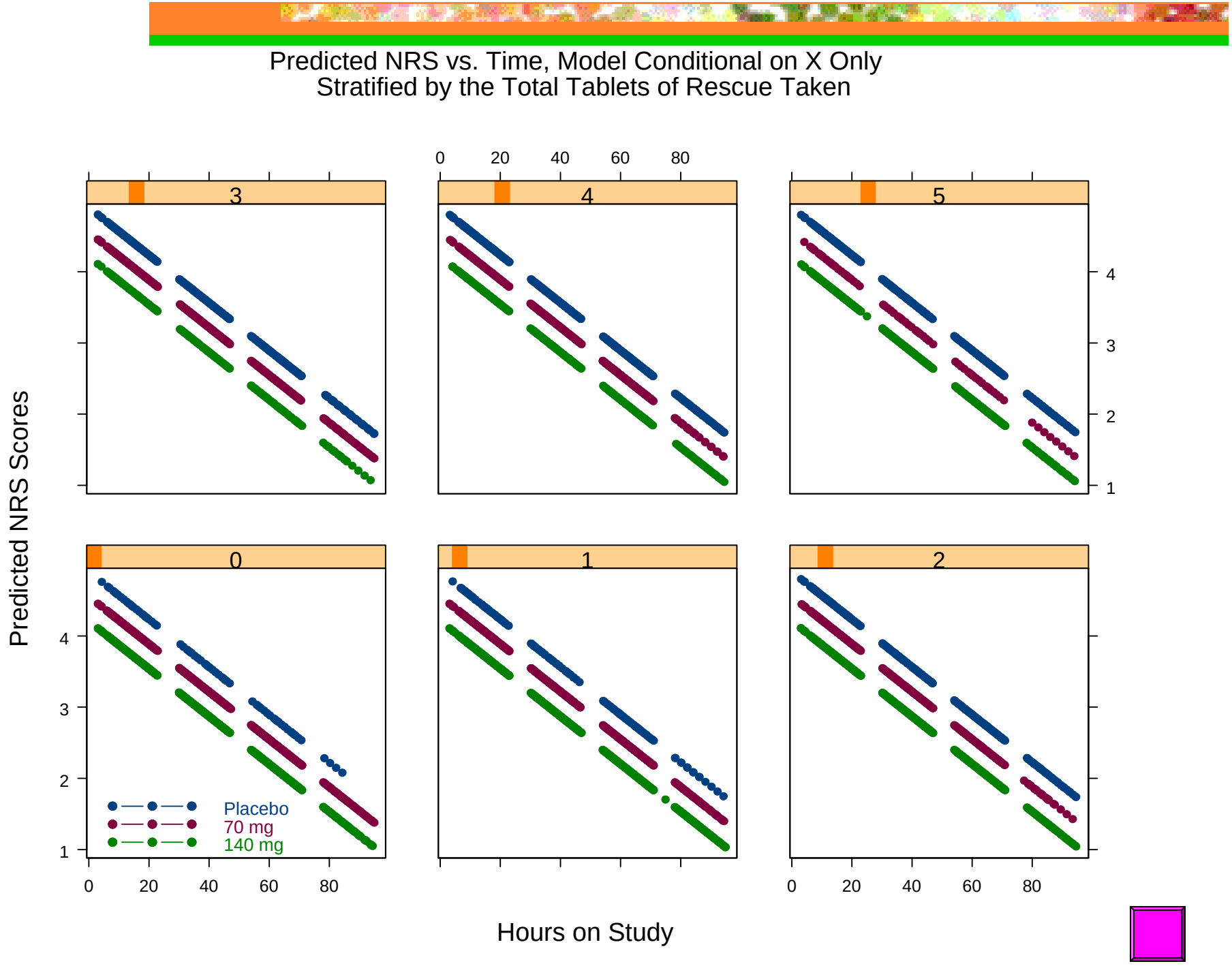
Conditional on rescue used, the treatment effect is virtually zero.

The total rescue used is matched exactly

The Second Model




Predicted NRS vs. Time
Model Conditional on X Only
Predicted NRS Scores
4
3
2
1
0
20
40
60
80
Hours on Study
Placebo
70 mg
140 mg


Predicted NRS vs. Time, Model Conditional on X Only
Stratified by the Total Tablets of Rescue Taken
Predicted NRS Scores
Hours on Study
3
4
5
0
1
2
Placebo
70 mg
140 mg

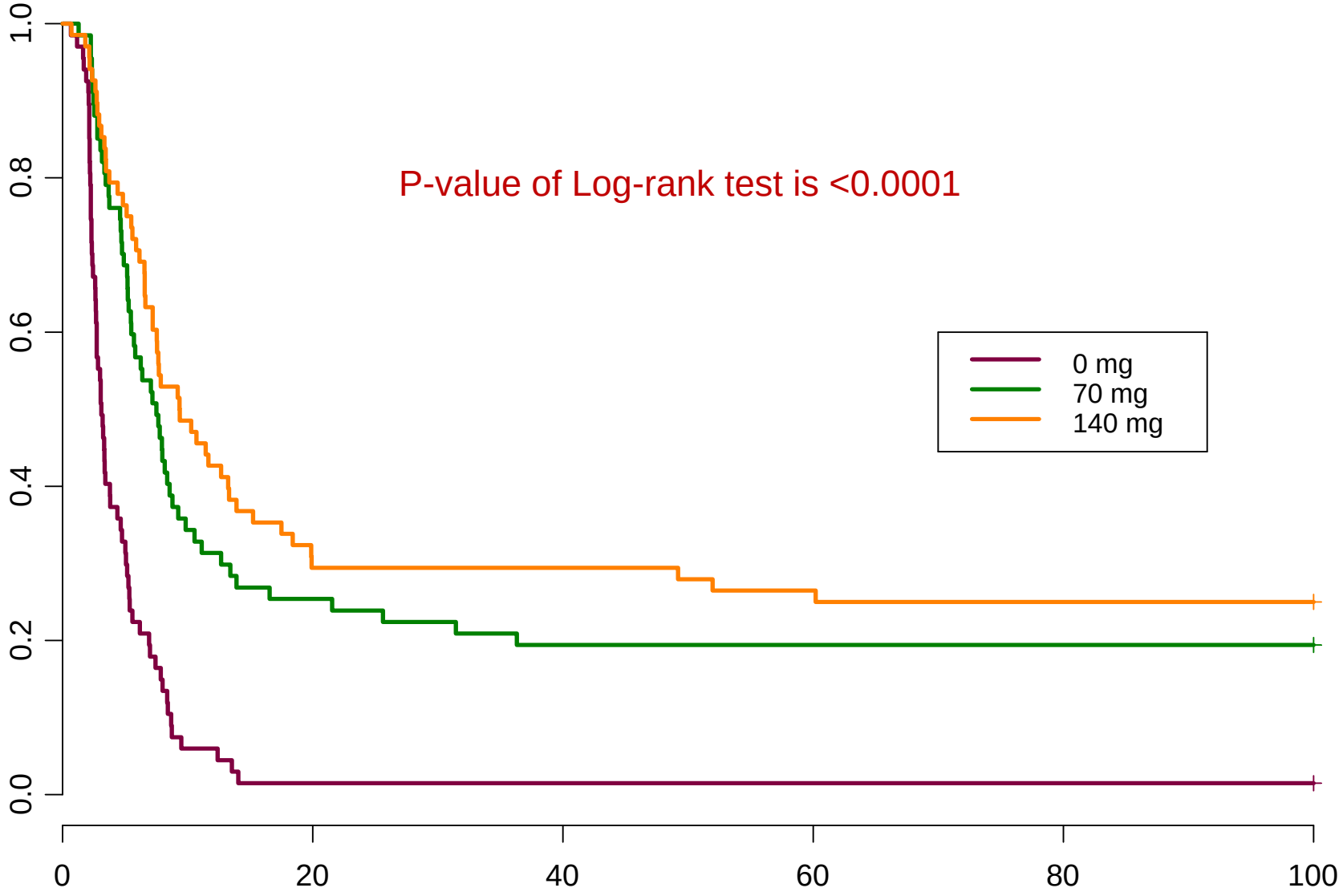
Estimated PTE

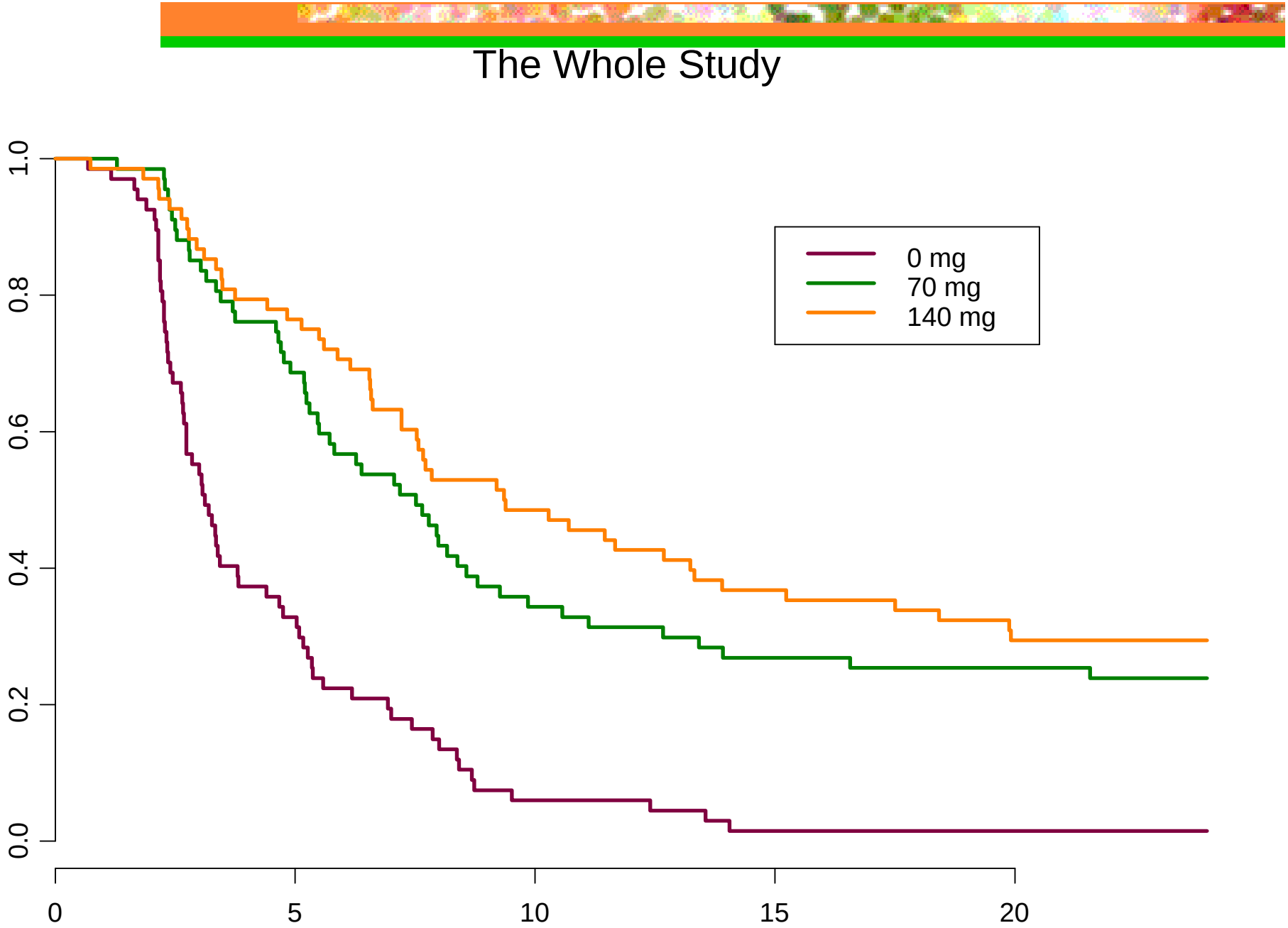
PTE is estimated to be 100%.

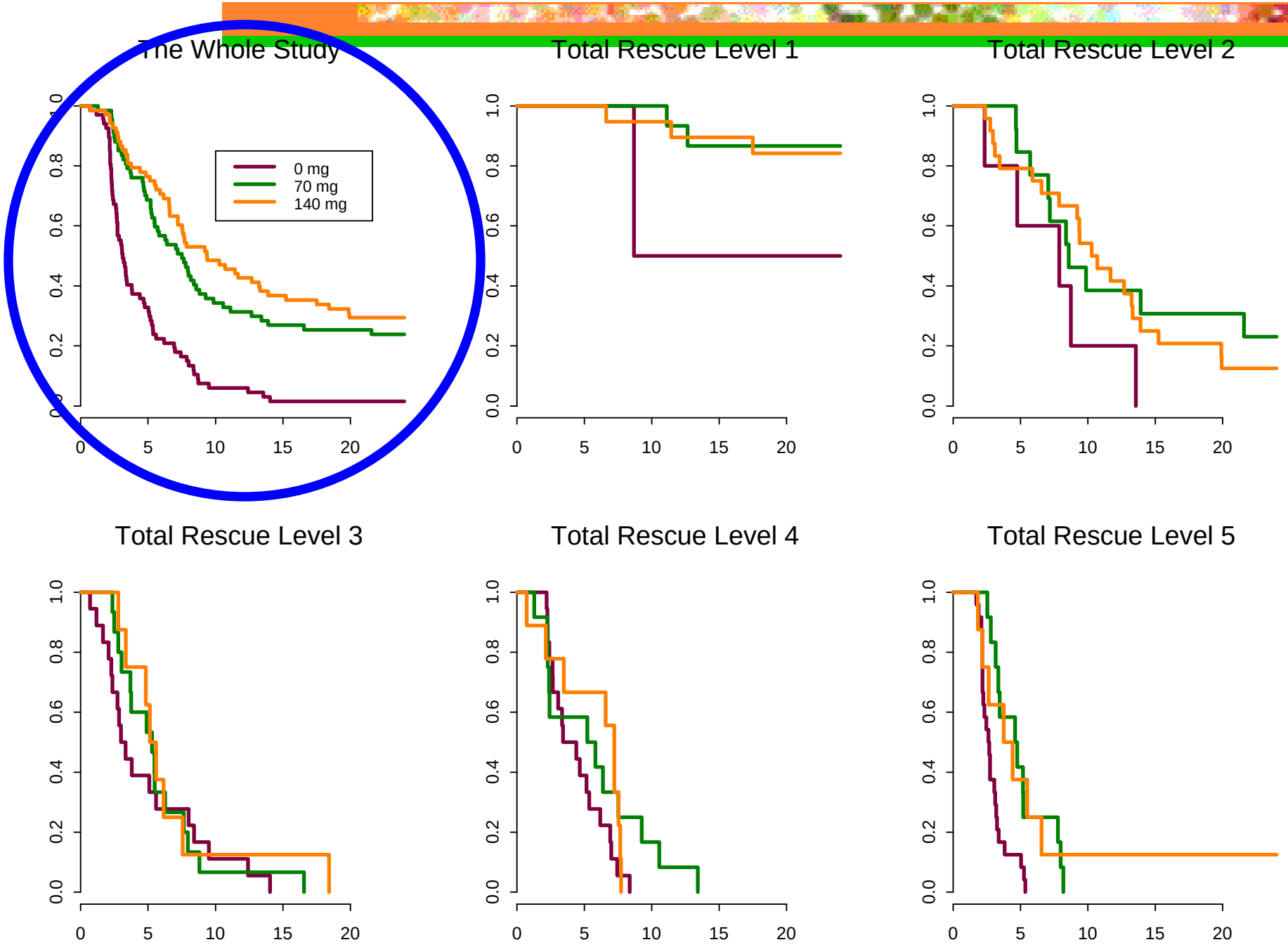
The Link between

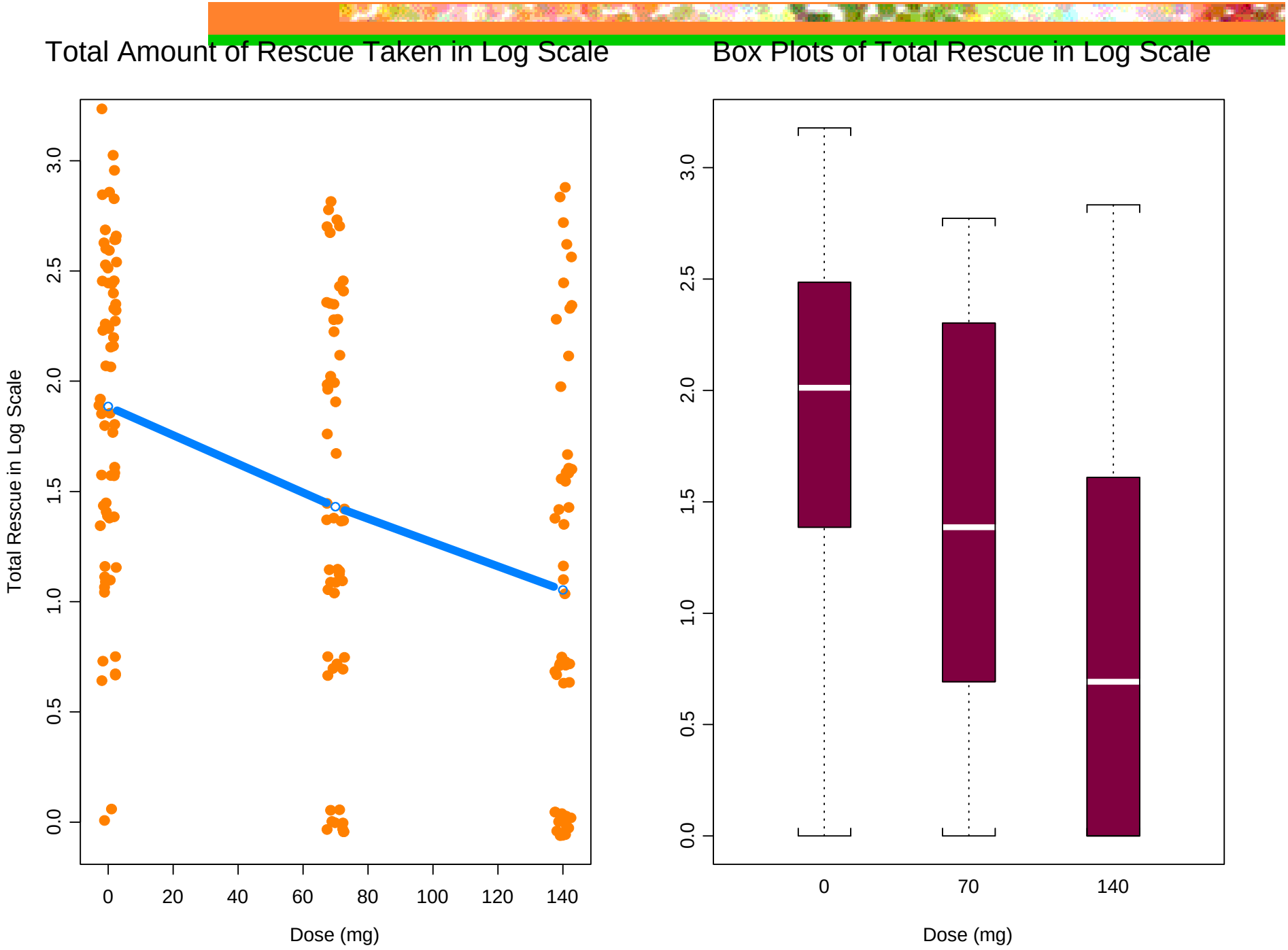
Scenarios 1 & 2

Kaplan-Meier Survival Curves for Time to Rescue
A Repeated-dose Acute Pain Study

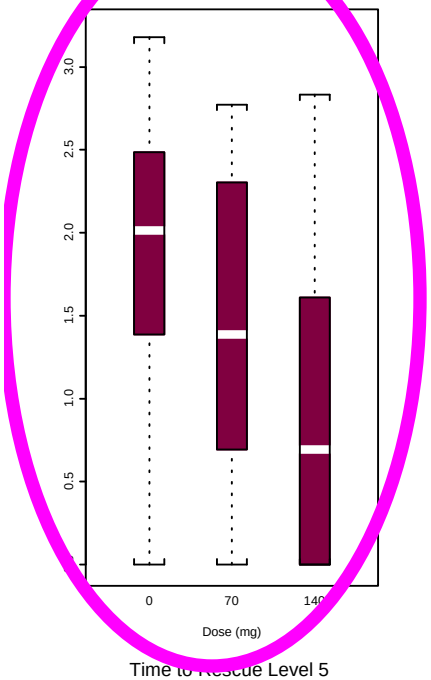



The Whole Study
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
0 mg
70 mg
140 mg

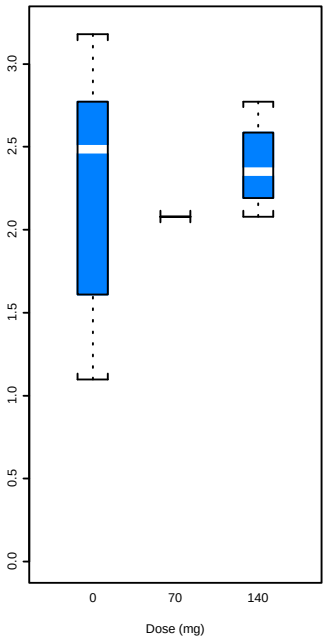

The Whole Study
0 mg
70 mg
140 mg
Total Rescue Level 1
Total Rescue Level 2
Total Rescue Level 3
Total Rescue Level 4
Total Rescue Level 5
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20


Total Amount of Rescue Taken in Log Scale
Total Rescue in Log Scale
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
20
40
60
80
100
120
140
Dose (mg)
Box Plots of Total Rescue in Log Scale
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
70
140
Dose (mg)

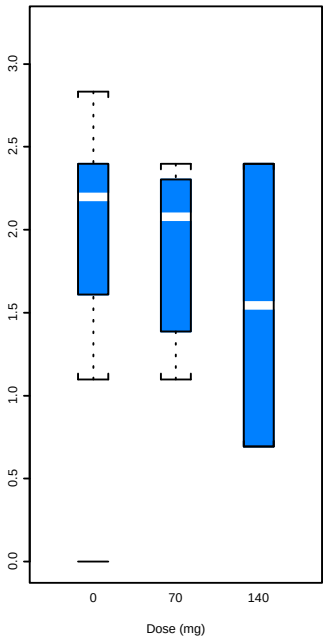
Total Rescue in Log Scale



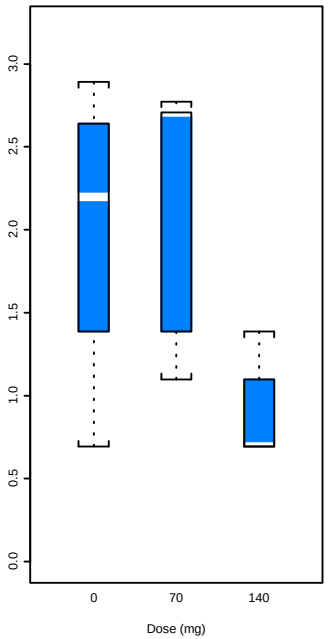
Time to Rescue Level 1



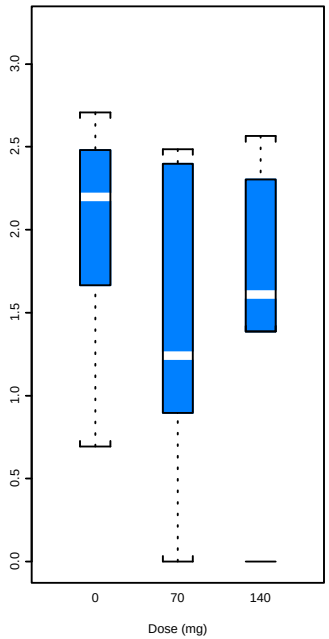
Time to Rescue Level 2



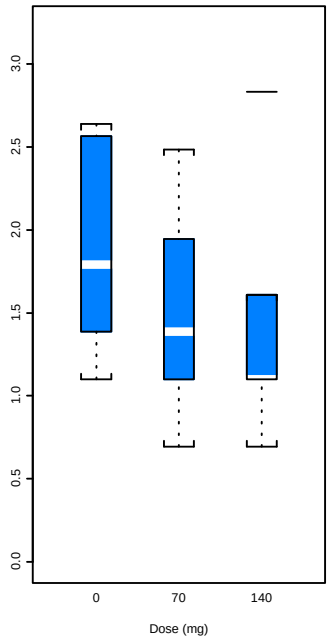
Time to Rescue Level 3



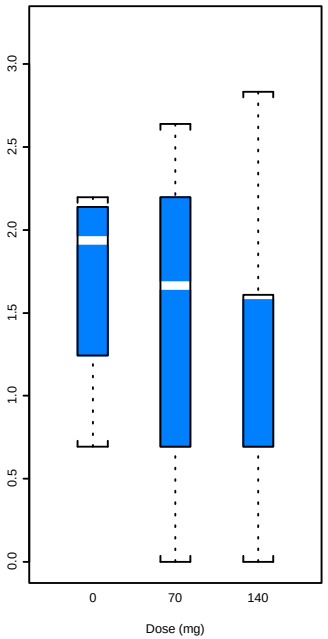
Time to Rescue Level 4



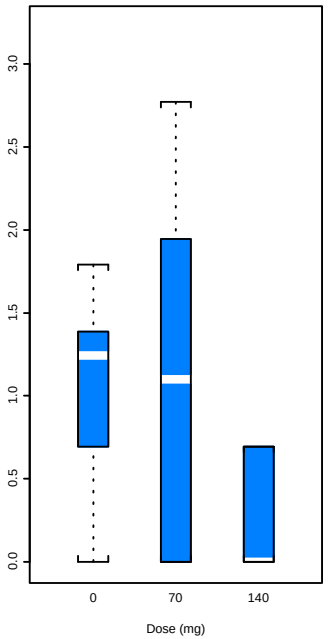
Time to Rescue Level 5



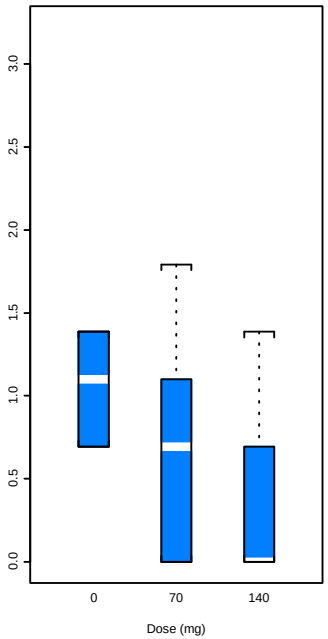
Time to Rescue Level 6



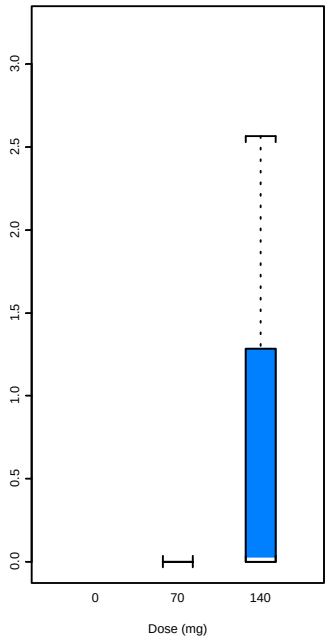
Time to Rescue Level 7

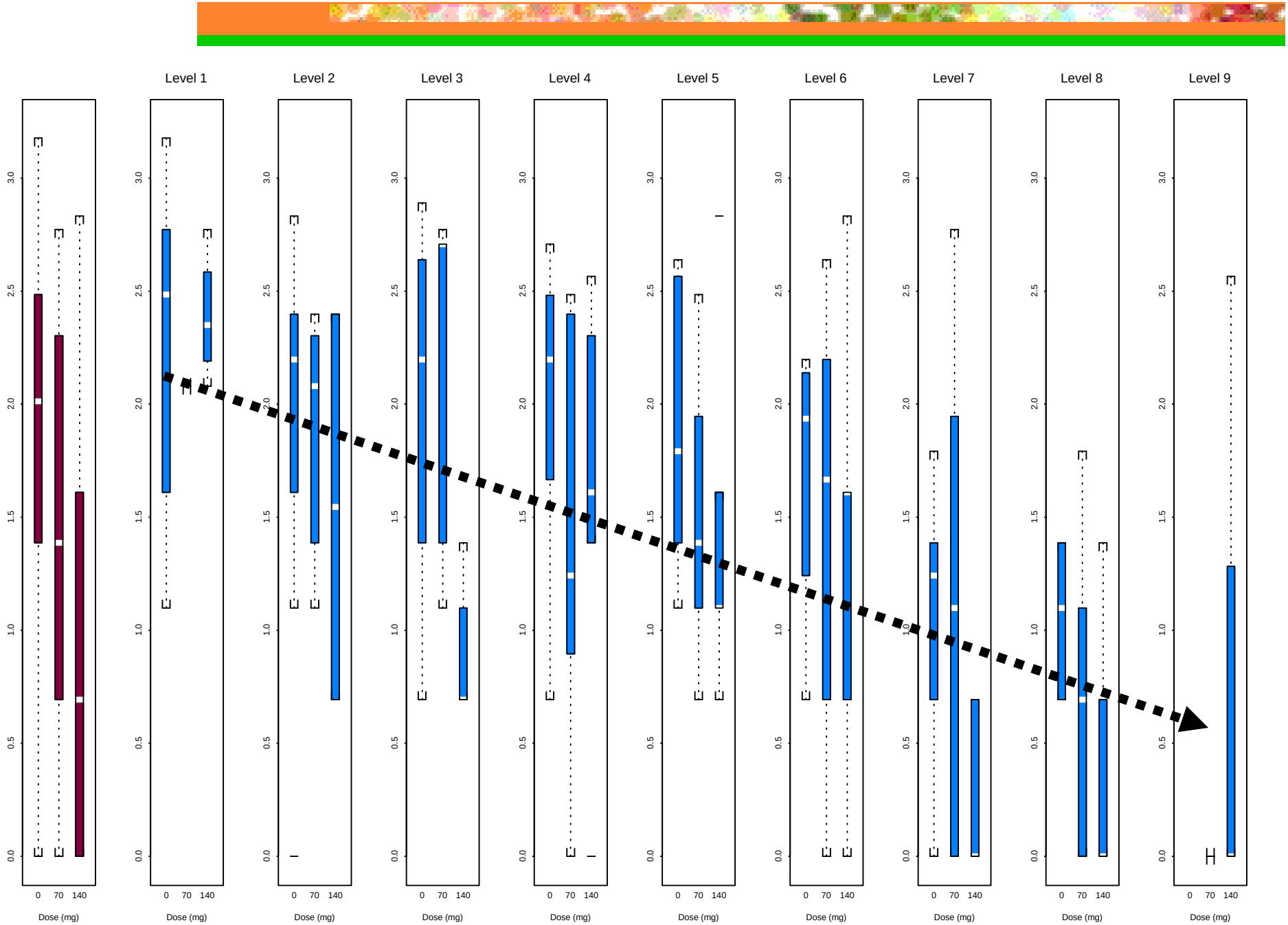


Time to Rescue Level 8



Time to Rescue Level 9




Level 1
Level 2
Level 3
Level 4
Level 5
Level 6
Level 7
Level 8
Level 9
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
70
140
Dose (mg)

The Link

- The time to rescue and the total rescue used are highly correlated.
- Both reflect subject's receptor sensitivity to study medication.
- The time to rescue most often captures the first dose efficacy.
- The total rescue used reflect the efficacy of the complete dosing regimen.

Which Design?

- Scenario 1 is appropriate for short single-dose studies
- Scenario 2 is suitable for longer repeated-dose studies.

Summary

- The conventional primary efficacy variables in acute pain studies are either plagued by missing values or influenced rescue medication.
- The time to rescue or total rescue used capture the efficacy information and serves as a surrogate for the longitudinally collected pain scores.
- Propose to adopt the time to rescue or total rescue used as the primary variable.