A Longitudinal Model and Graphic for Benefit-Risk Analysis, With Case Study

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Benefit-Risk Assessment is Hard

The following comments are from a 2011 Advisory Committee meeting on a first-in-class drug. The committee voted 9-6 against approval:

- *I voted no. I actually like this drug.*
- *I voted no, but it was the closest of calls. I changed my mind about four times in the last 10 seconds.*
- *I voted no. And I agree with all of my colleagues that voted both yes and no… I went back and forth and back and forth.*
- *I voted yes. I have a hard time disagreeing with almost everything that's been articulated here today.*

Why is it hard?

A non-exhaustive list:

- Benefits and harms (risks) are measured on different scales
- Many possible harms
- Missing data
- Benefit-risk tradeoff can change over time
- Benefits and harms may not be independent, e.g., active treatment responders may be at higher risk for adverse event (AE)

A Restricted Case

- Focus on treatments that provide mainly/entirely symptomatic relief, e.g., analgesics
- This simplifies handling of dropouts*. If they felt better on study treatment, would have probably stayed on it. (Non-medical reasons possible, but these are equally likely in all arms.)

*The same logic applies to patients who discontinue study treatment but stay in study, if this option is available.

Original Chuang-Stein model

- Introduced in Chuang-Stein, et al. (1991)*
- Each patient's outcome is one of following:
  1. Benefit, w/out adverse event (AE)**
  2. Benefit + AE
  3. Neither benefit nor AE
  4. AE only
  5. Early withdrawal due to AE
- Advantages: Deals with association between benefit and harm; addresses early discontinuation problem.

* Revised in Chuang-Stein (1994), but focus here on original model
** "Serious side effects"

Revised model

- Count all withdrawals equally (symptomatic relief)
- Consider benefit-risk as dynamic process, allowing patients to change state over course of trial

Application: Chronic Pain

- Mild-to-moderate severity AE's common
- Benefit is subjective
- High discontinuation rates. Traditional missing data methods arguably inapplicable, because nothing is really "missing".
- Might expect benefit-risk profile to change over time as patients develop tolerance for drug (opiate), adjust to side effects, etc.
- Perception that current trial designs are inadequate to show true efficacy (ACTTION initiative)

Case Study #1 Hydromorphone

- Extended-release hydromorphone (HM) tablet approved March 2010. I was the primary stat reviewer.
- Advisory committee considered risks of abuse and diversion. Did ***not*** attempt to model these risks.

Study Design

- 12-week DB trial. Pain recorded daily on 11-point rating scale ("No pain" → "Worst Possible pain").
- Randomized withdrawal design – patients titrate to effective dose, then randomized to active drug or matching placebo
- 58% of subjects were titrated to effective dose and randomized
- Limited amount of rescue medication

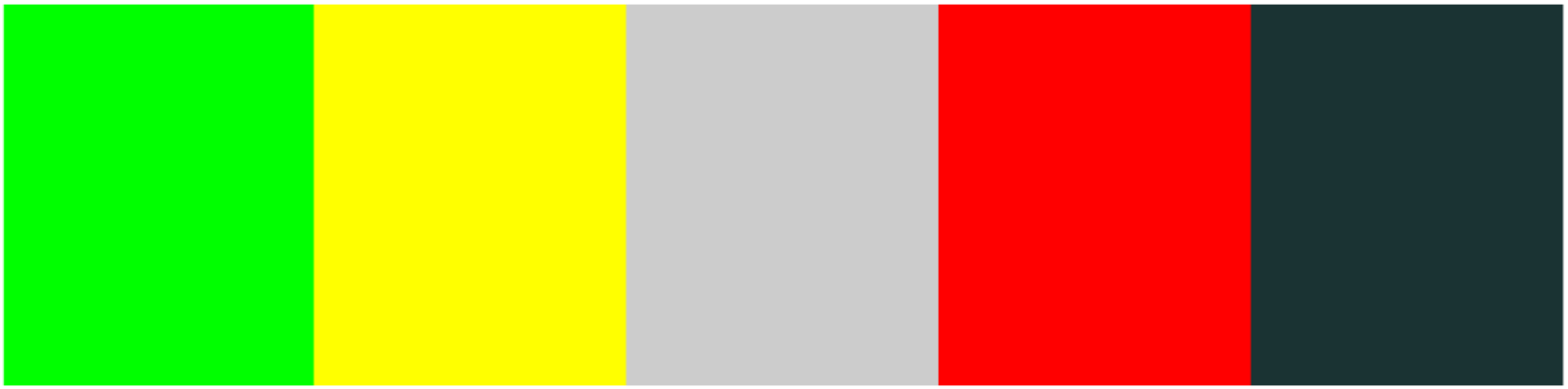
Chuang-Stein model for HM Study

- Benefit = 30% reduction in pain from screening baseline (Farrar et al, 2001)
- AE = moderate-to-severe adverse event in DB phase of study

Individual Response Profile

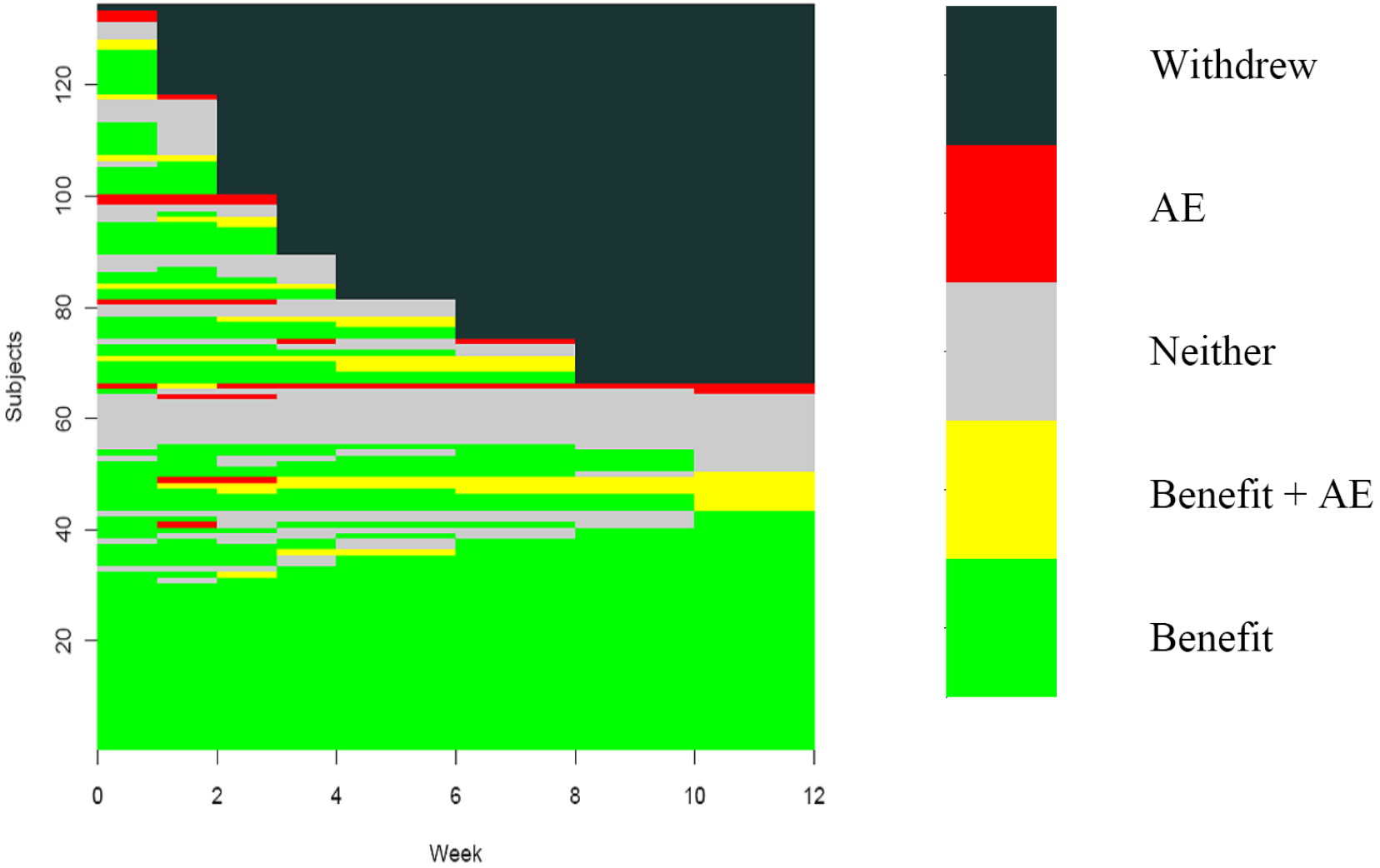
- IRP graphic has **one row for each subject**
- X-axis is time
- Colors used to distinguish individual states
- Sort rows for clarity. Preferred method uses last period as primary sort key, then second-to-last period, etc.
- Could be used for any longitudinal, categorical study outcome, not just Chuang-Stein model
- Similar graphics: event history (Dubin et al, 2001), safety at FDA (Szarfman et al, 1997), lasagna plots (Swihart et al, 2010)

Legend

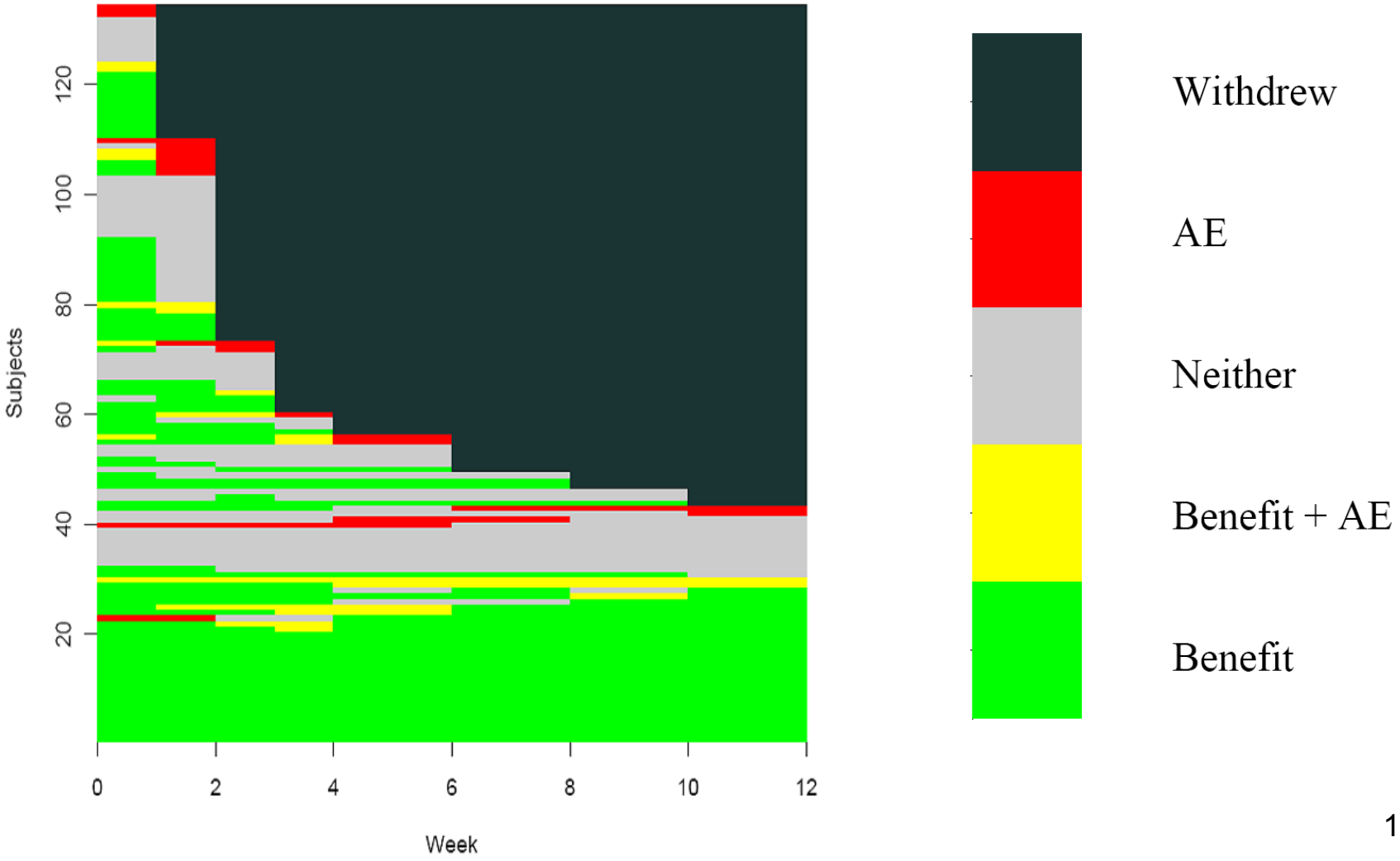


Note: Color-blind accessible figures start on slide 38.

HM Results

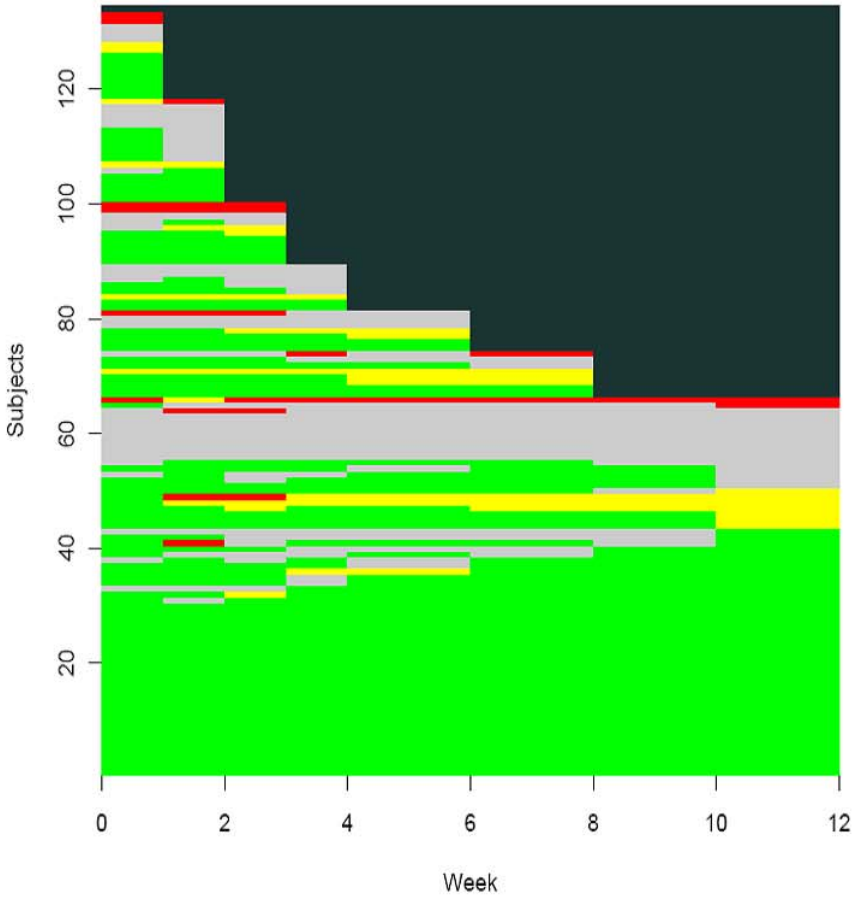

Subjects
20
40
60
80
100
120
0
2
4
6
8
10
12
Week
Withdrew
AE
Neither
Benefit + AE
Benefit

Placebo Results

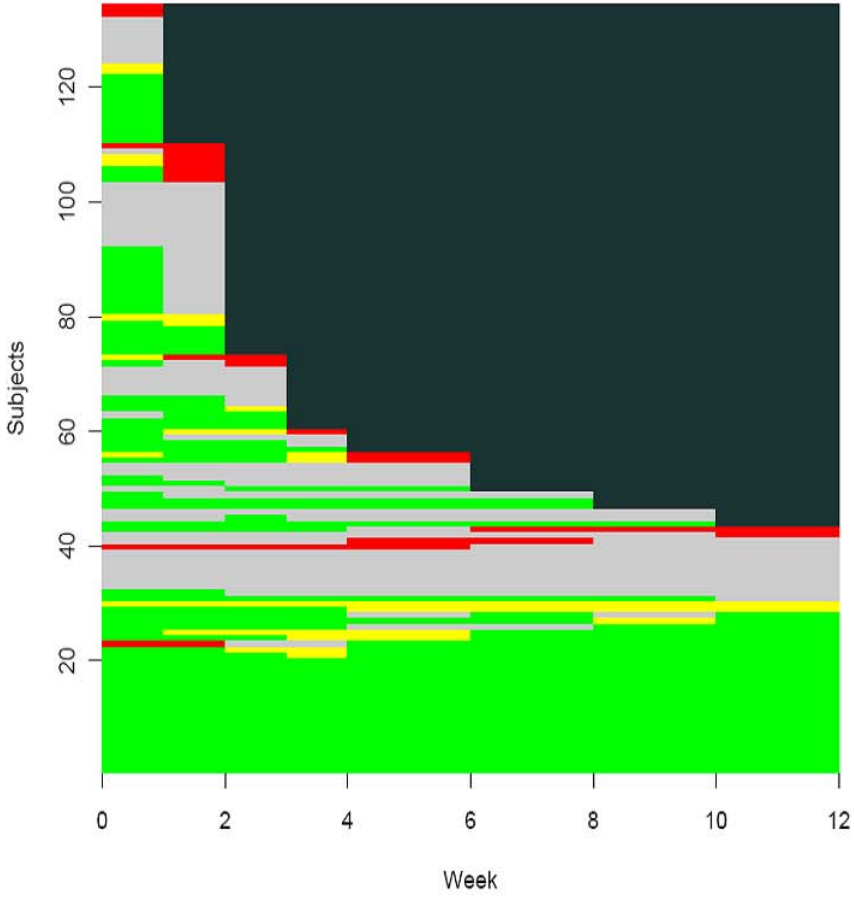


Comparison of IRPs

HM



Placebo



Additional Case Studies

Joint with Sanatan Saraf, FDA Intern

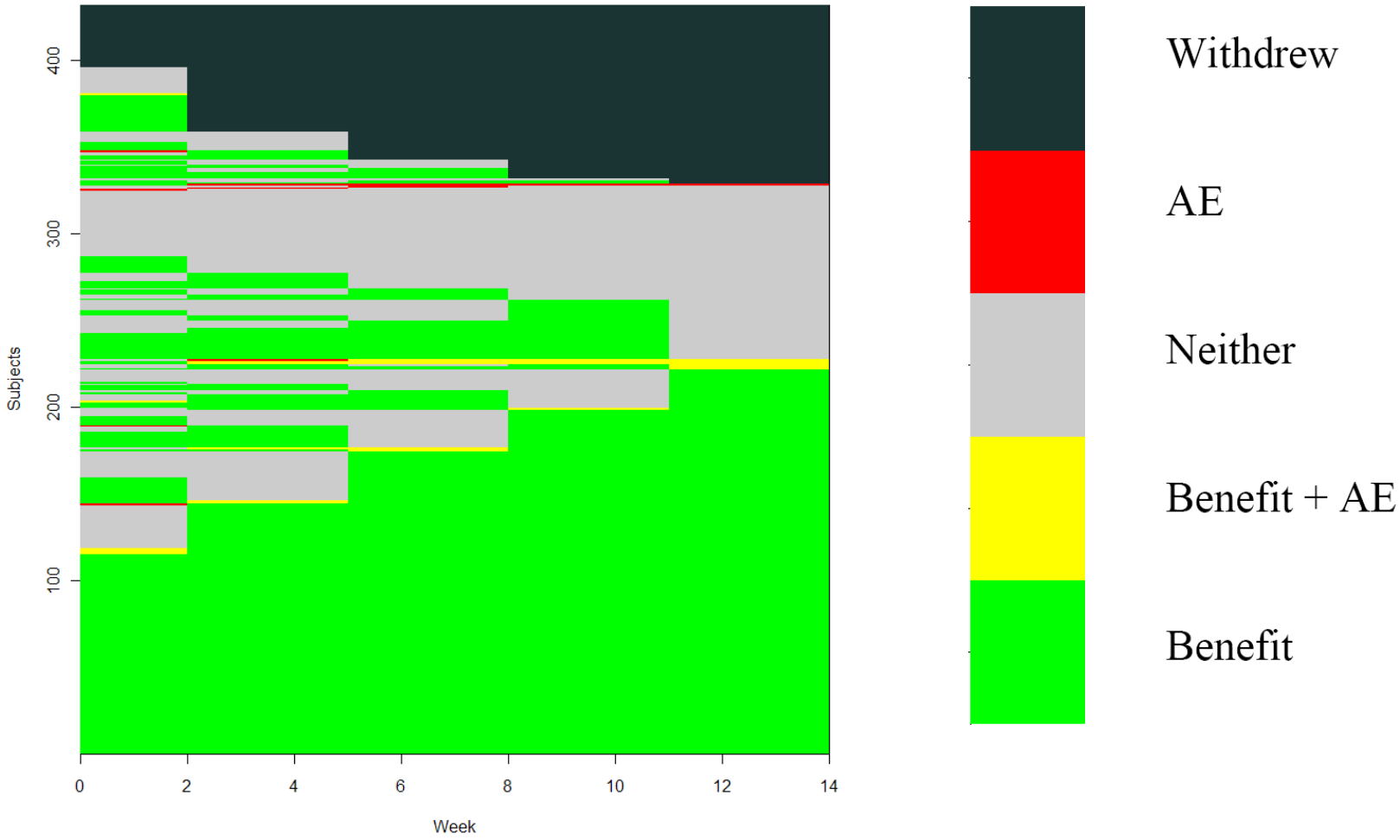
Case Study #2: Tramadol

- Extended-release tramadol approved in 2008
- Weak opiate with other modes of action. Genetic polymorphism (CYP2D6) affects metabolism.
- Design – also randomized withdrawal:
  - 4 wk OL: 2 wk run-in, 2 wk taper and washout
  - 14 wk DB: 2 wk titration, then 12 wk maintenance
  - 63% of treated patients were randomized

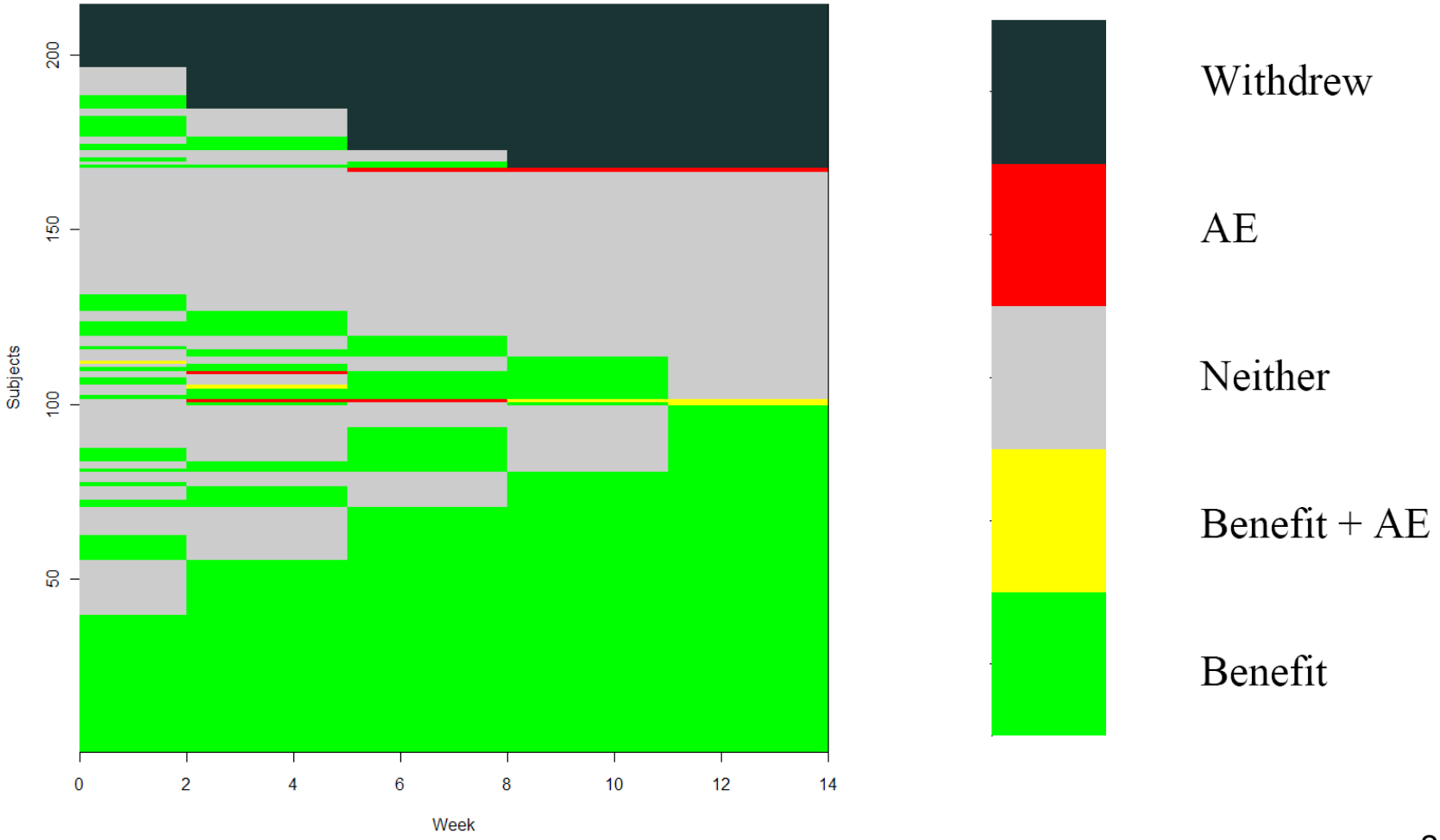
Tramadol (cont.)

- Benefit: 30% reduction in pain from end of washout
- Risk: All severe or serious AEs
  - Onset must be in DB period
  - Broader inclusion criteria for AE used in manuscript in development
- Not “apples to apples” comparison with HM. Drugs would essentially have to be on same protocol for fair comparison.

Tramadol


Subjects
100
200
300
400
0
2
4
6
8
10
12
14
Week
Withdrew
AE
Neither
Benefit + AE
Benefit

Placebo


Subjects
200
150
100
50
0
2
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6
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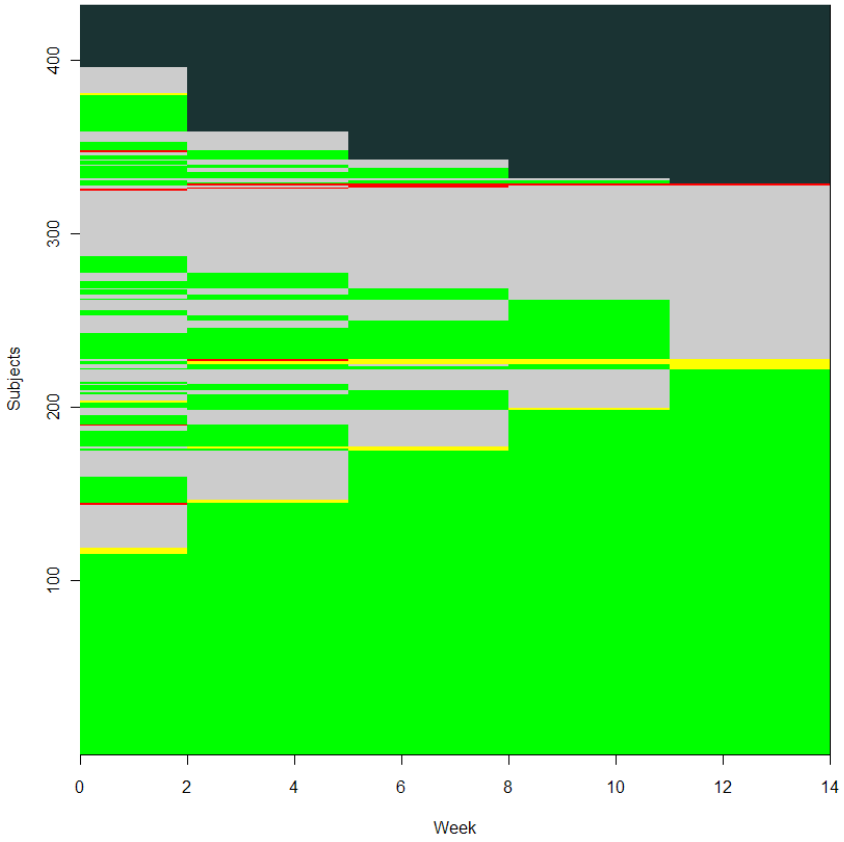
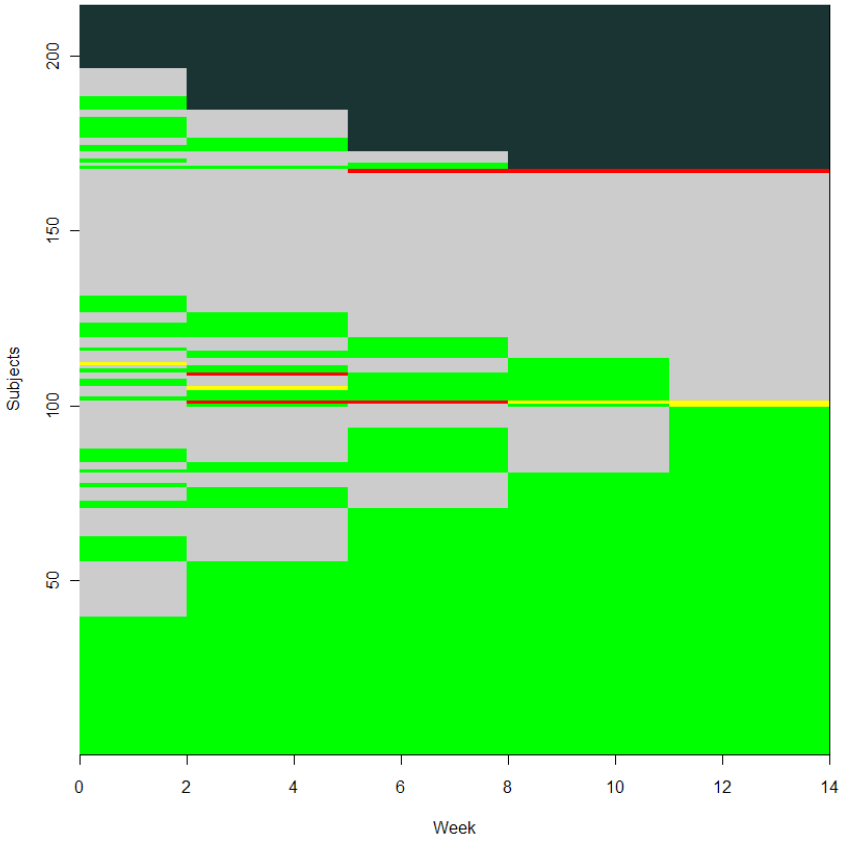
10
12
14
Week
Withdrew
AE
Neither
Benefit + AE
Benefit

Comparison

Tramadol



Placebo



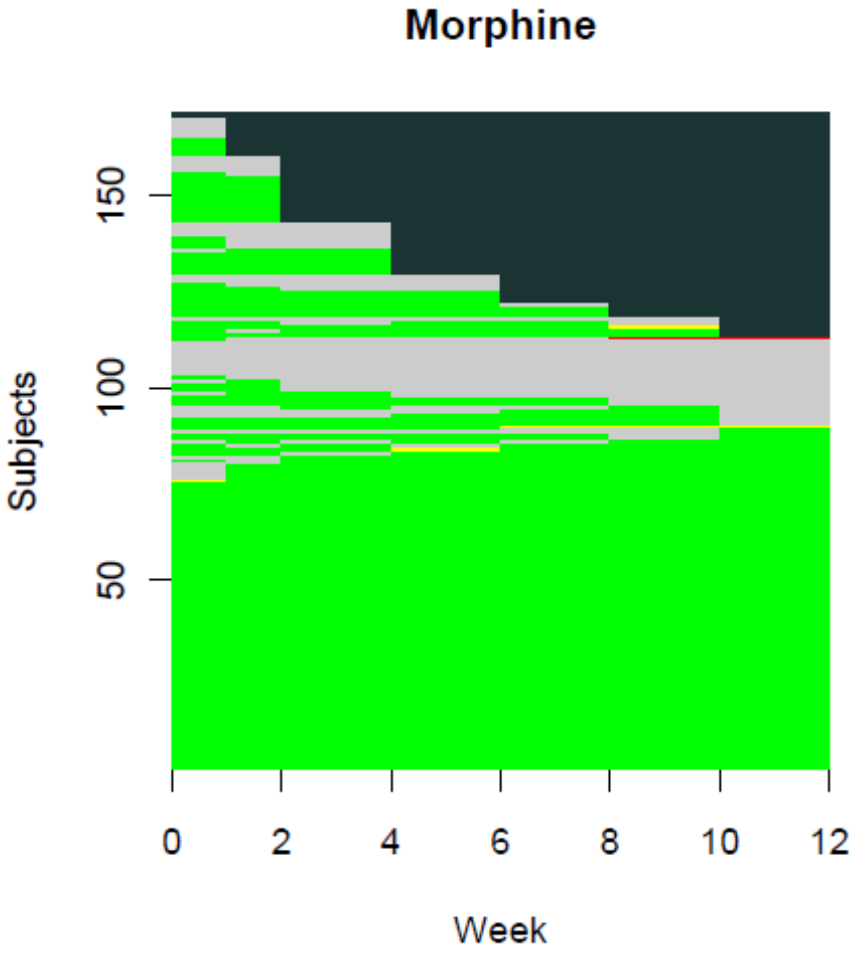
Case Study #3: Morphine

- Extended-release morphine approved in 2009
- Design – also randomized withdrawal:
  - 9 wk OL: 2 wk screening, 1 wk washout and 6 wk Titration period
  - 12 wk DB: 12 wk maintenance
  - 62.9% (344/547) of patients who entered titration period were randomized

Morphine (cont.)

- Same definitions of Benefit and Risk as tramadol
- Again, not “apples to apples” comparison with other cases

Comparison


Morphine
Subjects
150
100
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2
4
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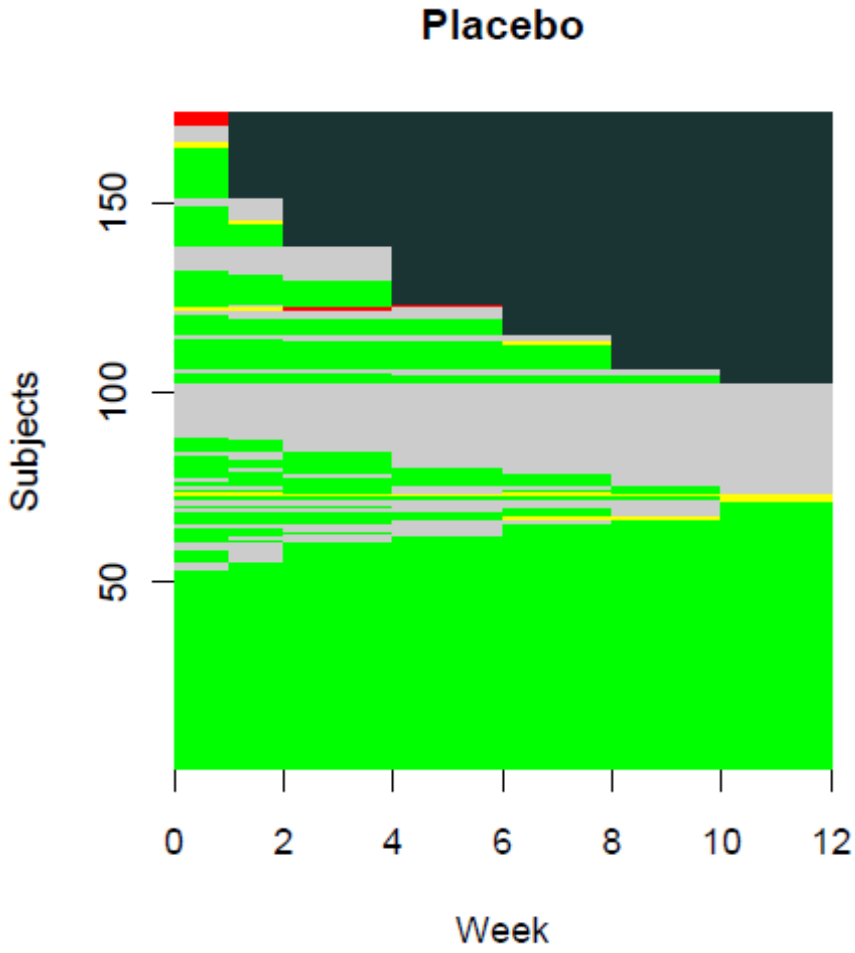
8
10
12
Week


Placebo
Subjects
150
100
50
0
2
4
6
8
10
12
Week

Testing

- Temporal correlations
- Hard to avoid assigning score to each category and weight to each time period
- One approach: Weighted sum of *signed* Pearson correlation coefficients, with *r* the correlation between the treatment indicator and the outcome for a period. Use permutation test.

Testing (cont.)

$$S = \sum_{t=1}^{T} w_t Y_t$$

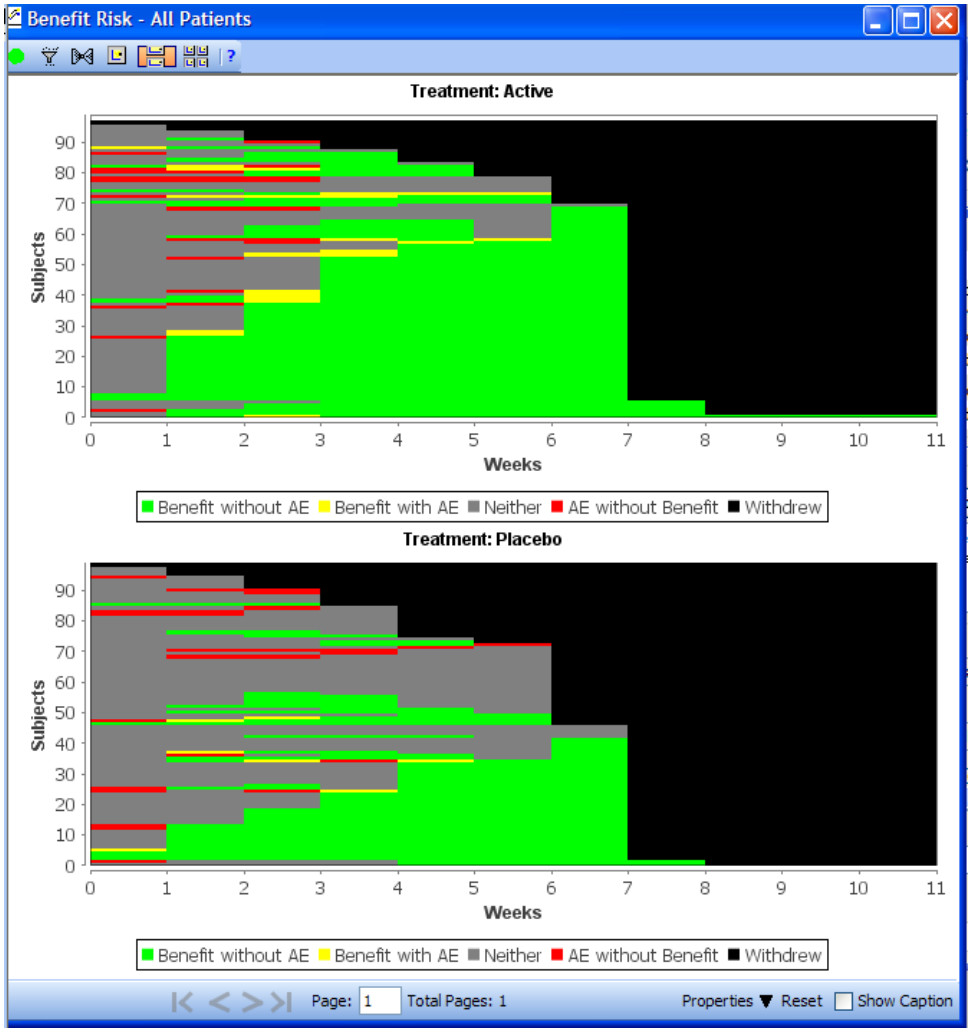
where *S* is test statistic, *w* weight on period t, *Y* is score for outcome on period *t*

- Ad-hoc approach:
  - o Equal spacing for categories, e.g., $Y \in \{1,\ldots,5\}$
  - o Linearly increase weight over course of trial
- Applying ad-hoc test to HM, for example, superior to placebo with *p* = .0011 (permutation)

Software Implementation

- IRP feature in development for JReview software (Integrated Clinical Systems, Inc.)*

**Figure courtesy of ICS. No financial relationship with speaker.*

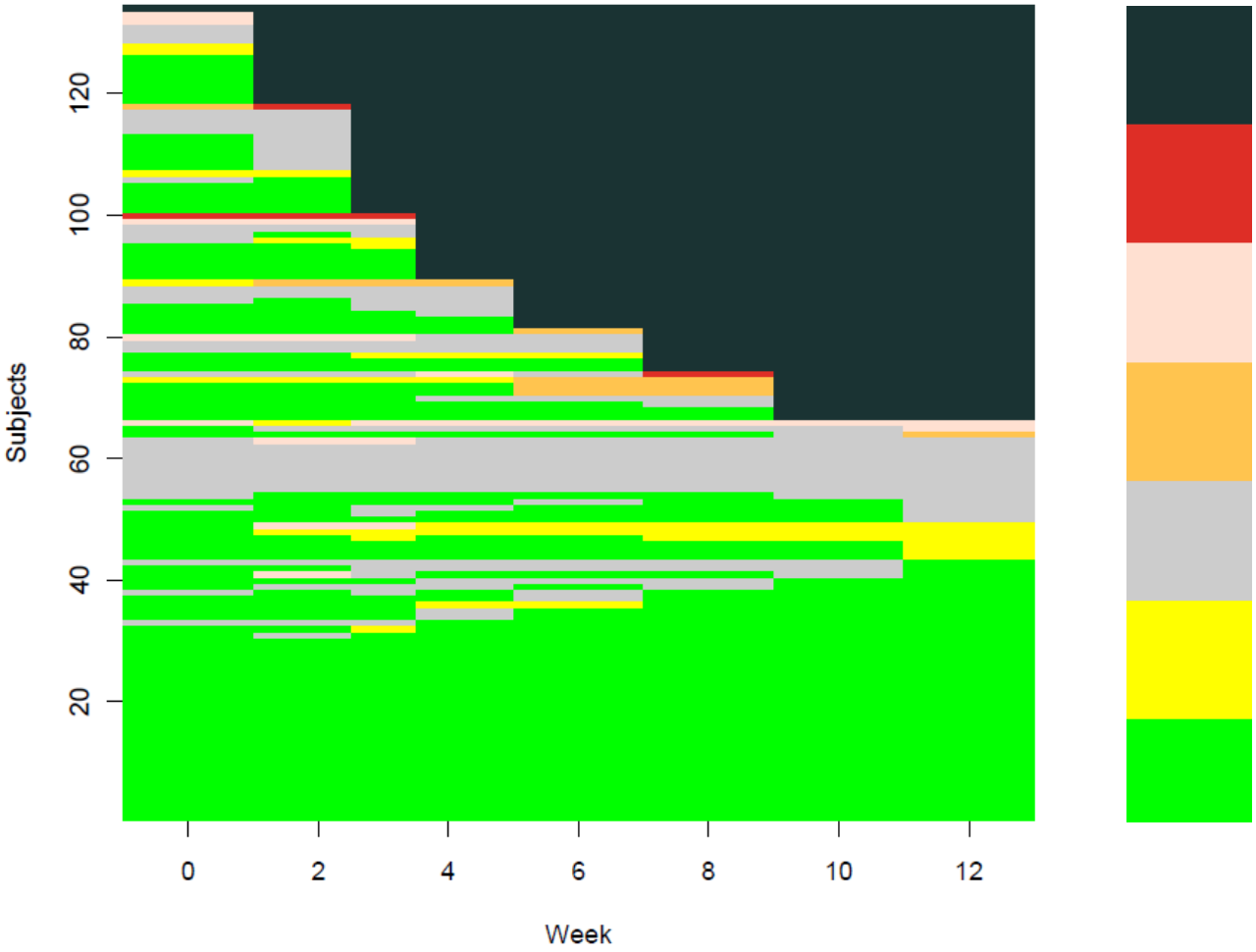


More Colors?

- Frequent suggestion is to use more colors to indicate the severity of an AE
- My preference is for simplicity
- However, here is one possible scheme:

Benefit	Benefit + Mod. AE	Neither	Benefit + Sev. AE	Mod. AE	Sev. AE	Withdrew

HM – With severity



Concluding Opinions

- The human mind can only handle a certain amount of information. Tools like the IRP can help to reduce a complex problem to manageable chunks.
- Statisticians, clinicians, psychologists, and other should collaborate on developing these tools. Many dissertations could be written.
- Transparency in decision making is ultimately beneficial to everyone.

Acknowledgments

- Sanatan Saraf (FDA intern, also University of Maryland, Baltimore County)
- Frank Pucino, Pharm.D. (FDA)
- Tom Permutt, Ph.D. (FDA)
- Ana Szarfman, M.D., Ph.D. (FDA)
- FDA for Regulatory Science And Review Enhancement grant
- Drug sponsors for providing data

References

- Chuang-Stein, Mohberg, Sinkula (1991). *Stat Med.* 10:1349-1359.
- Chuang-Stein (1994). *Contr Clin Trials*. 15:30-43.
- Dubin, Muller, Wang (2001). *Stat Med.* 20:2951-2964.
- Farrar et al (2001). *Pain*. 94:149-158.
- Swihart et al (2010). *Epidemiology*. 21:621-625.
- Szarfman, Talarico, Levine (1997). *Comprehensive Toxicology.* 4:363-79. Ed: Sipes, McQueen, Gandolfi.

Additional Slides

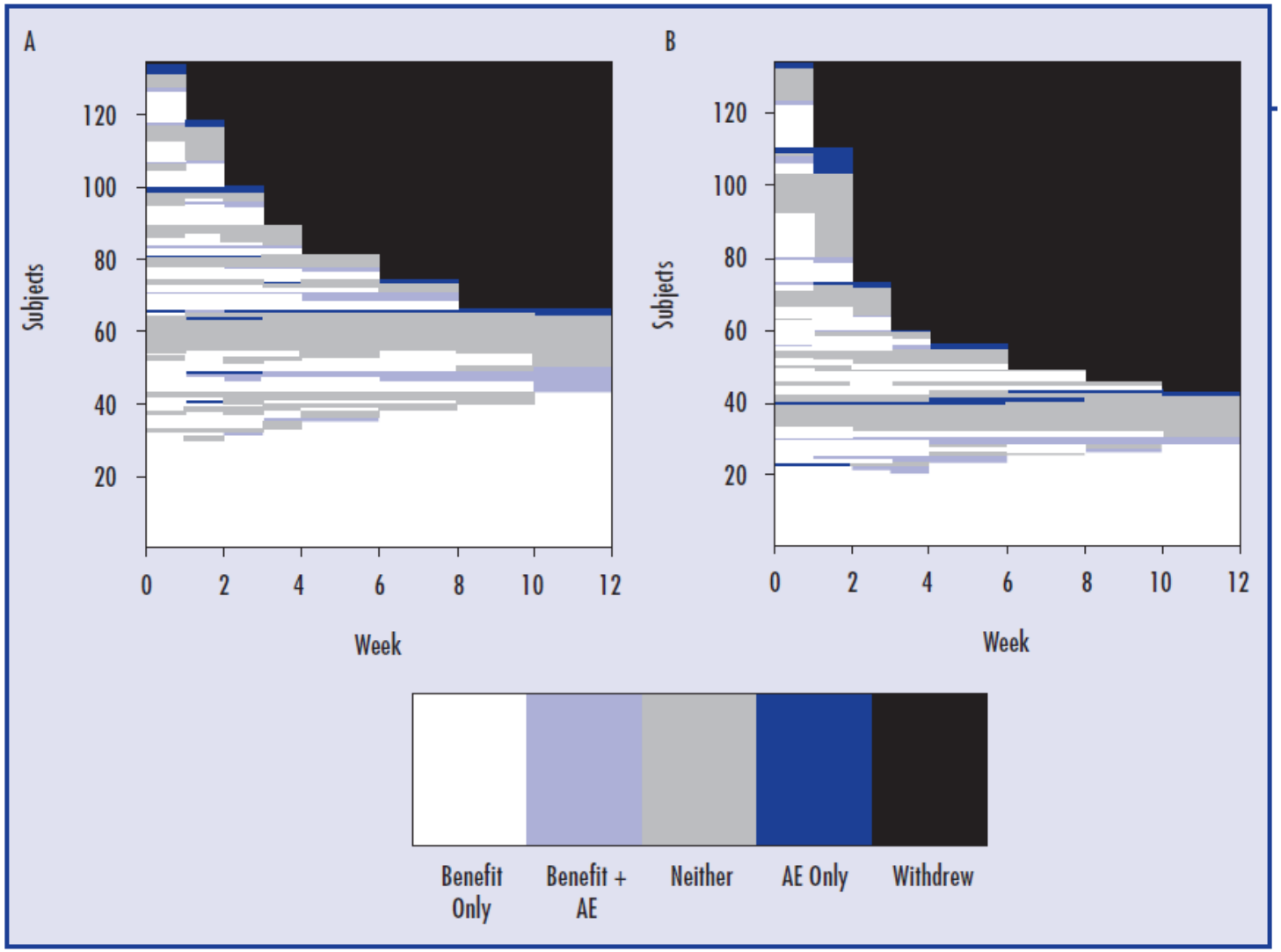
Sample Code

Plotting in R

```
#Notes: Tested in R 2.10.1. Use at your own risk.
library(graphics)
#Toy example with three 4-week time periods and two subjects
Weeks <- c(0,4,8,12)
#Subject 1 was in yellow state, then gray, then red
Subj1 <- c(2,3,4)
#Subject 2 was in green state, then yellow, then withdrew
Subj2 <- c(1,2,5)
Outcomes <- as.matrix(rbind(Subj1, Subj2))
#Sort matrix, using final period as primary key, then using second-to-last period, etc.
SortedOutcomes <- Outcomes[order(Outcomes[,3],Outcomes[,2],Outcomes[,1]),]
nsub <- dim(Outcomes)[1]
stoplightcol <- rgb(c(0,1,.8,1,.1),c(1,1,.8,0,.2),c(0,0,.8,0,.2))
image(Weeks,1:nsub,t(SortedOutcomes),col=stoplightcol)
#accessible purple-gray scheme
accessiblecol <- rgb(c(.75,1,.5,.5,0),c(.75,0,.5,0,0),c(.75,1,.5,.5,0))
image(Weeks,1:nsub,t(SortedOutcomes),col=accessiblecol)
```

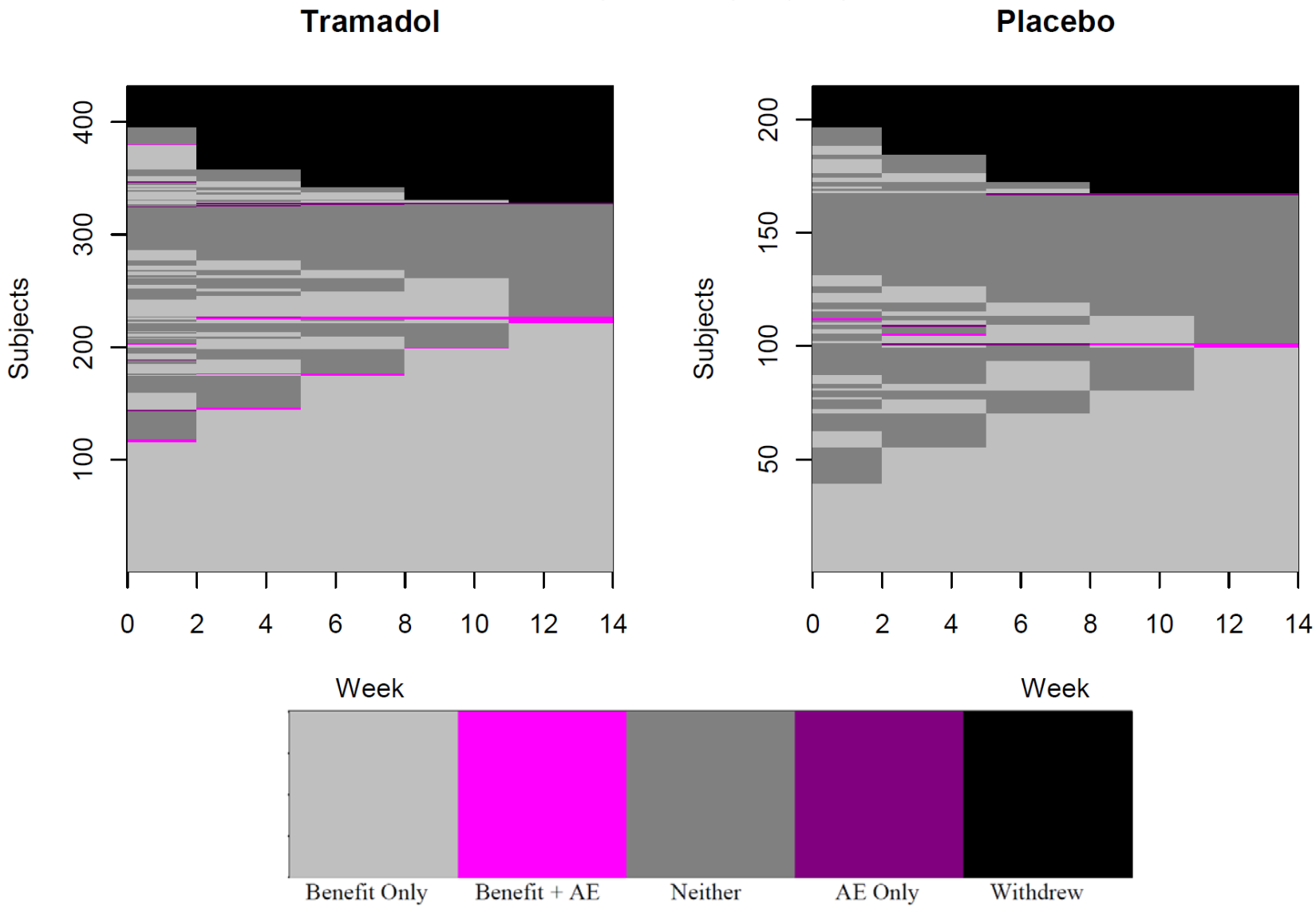
Color-Blind Accessible Figures

Hydromorphone



A: HM
B: Placebo

Tramadol


Tramadol
Placebo
Subjects
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4
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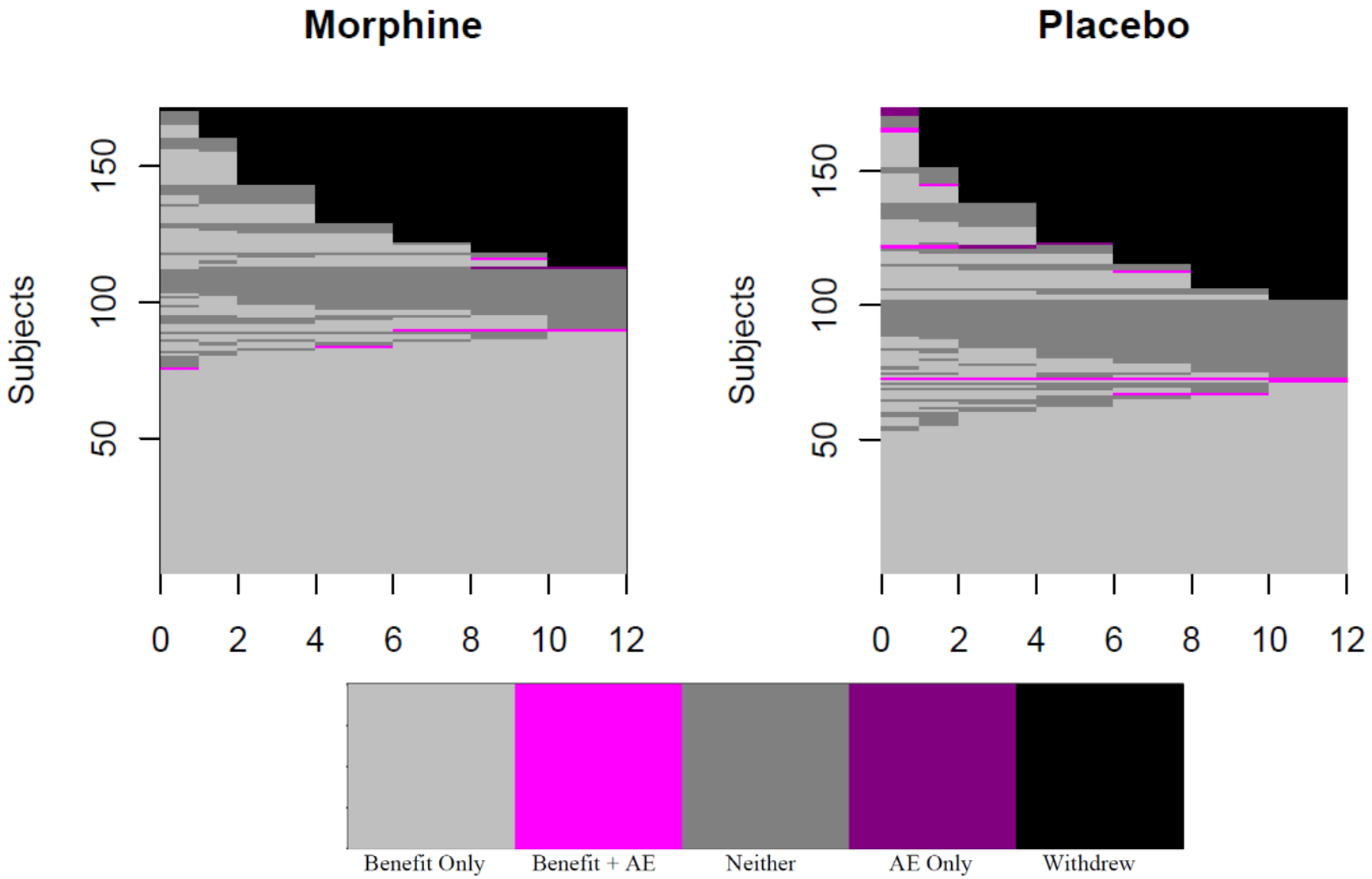
8
10
12
14
Week
Benefit Only
Benefit + AE
Neither
AE Only
Withdrew

Morphine


Morphine
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Subjects
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