# Missing Data Mechanisms in a Dose Finding Adaptive Trial

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# Outline

- background
  - Sample size
  - Hypotheses
  - Study Design
  - Anastasia Ivanova's "Maximizing Procedure" Stat Med (2009)
  - Utility function
- missing data mechanisms
  - MCAR, MAR, NMAR, Mixture Missing Mechanism
- simulation results
- study results
- conclusion

# Sample Size Considerations

| Goal | Design | N / arm | Total N |
|---|---|---|---|
| Better than placebo | Parallel 2 arm | 69 | 138 |
| | X-over 2-period | 18 | 36 |
| + at least as good as Active Control | Parallel 3 arm | 270 | 810 |
| | X-over 3-period | 46 | 138 |
| + Dose finding among 5 doses | Parallel 7 arm | 270 | 1890 |
| | X-over 3-period | 46 | 690 |
| + Constraint of N < 200 | "Maximizing Procedure" using a 3-period X-over | NA | 200 |

# Hypothesis Summary

Primary hypothesis

Main goal: Mode and Top 2 adjacent doses vs Active Control

| Hypothesis | Endpoint | Mode dose vs Pbo | Top 2 doses vs AC | AC vs Pbo |
|---|---|---|---|---|
| Primary | Primary End | p-val | - | - |
| Secondary | Primary End<br>Sec End 1<br>Sec End 2 | -<br>p-val<br>p-val | CI for NI<br>-<br>- | -<br>-<br>- |
| Exploratory: Exploratory End 1, Exploratory End 2, Exploratory End 3, Exploratory End 4, … | | | | |

# Study Design
# 3-Period, 6-Sequence Crossover

| Sequence | Period 1 | WO | Period 2 | WO | Period 3 |
|----------|----------|----|----------|----|----------|
| 1 | MK | | Pbo | | AC |
| 2 | Pbo | | AC | | MK |
| 3 | AC | | MK | | Pbo |
| 4 | MK | | AC | | Pbo |
| 5 | Pbo | | MK | | AC |
| 6 | AC | | Pbo | | MK |

# "Maximizing Procedure" Example

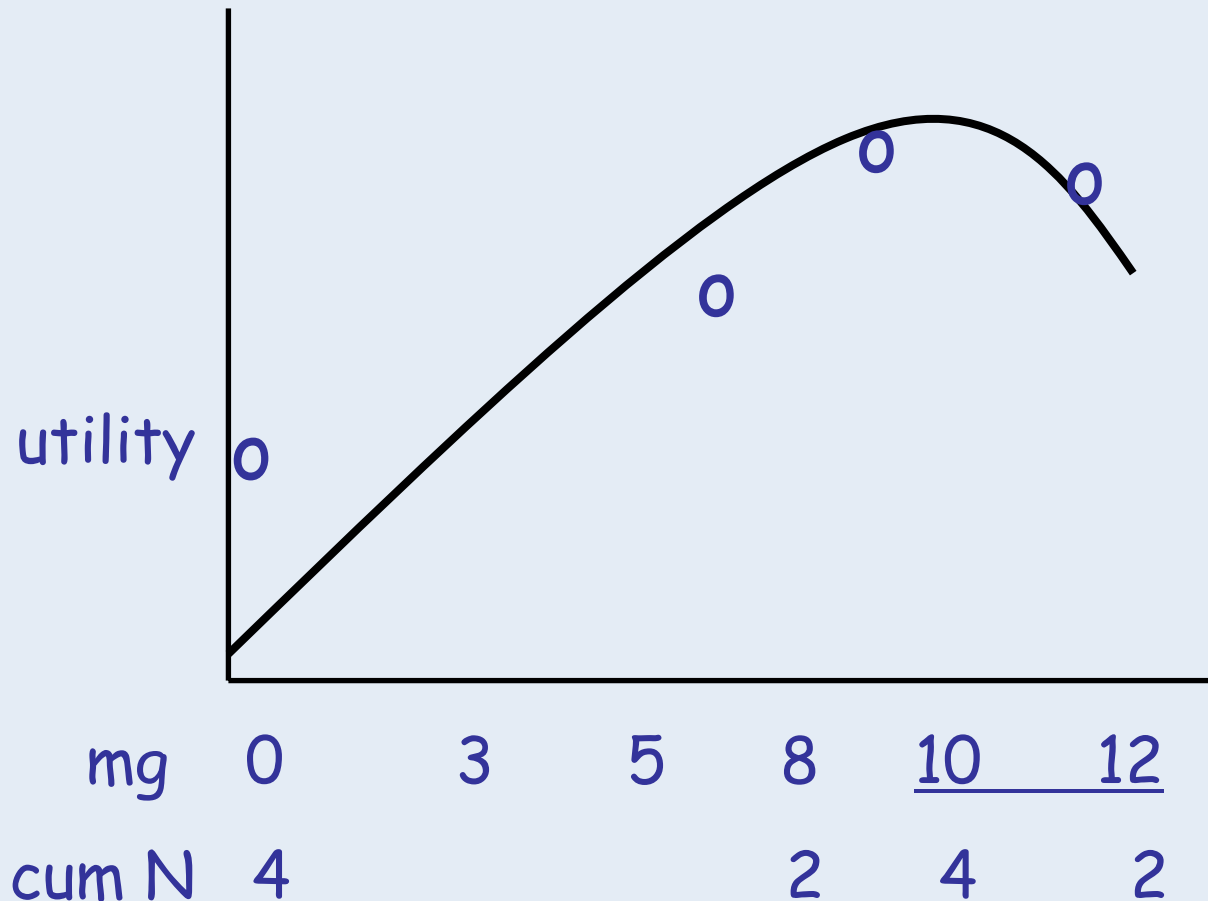

true
utility

mg    0     3     5     8    10    12
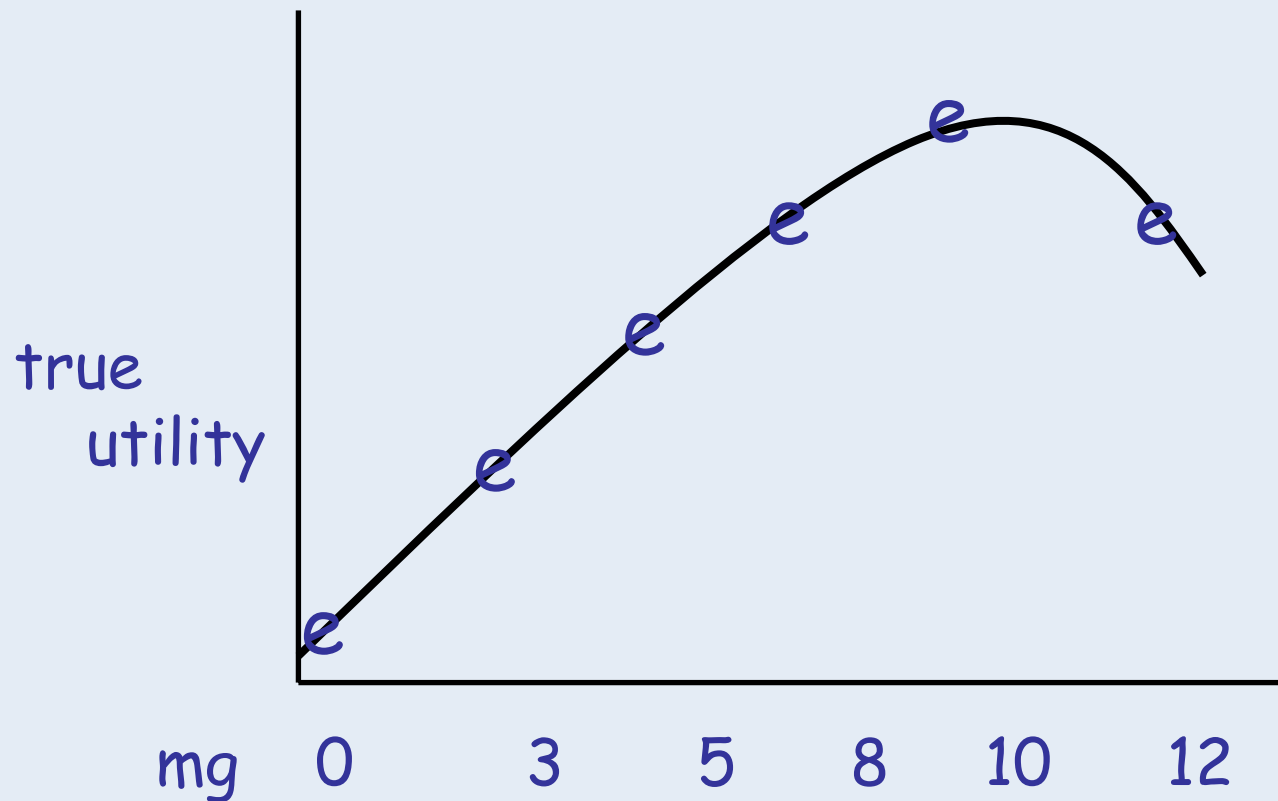
# "Maximizing Procedure" Example
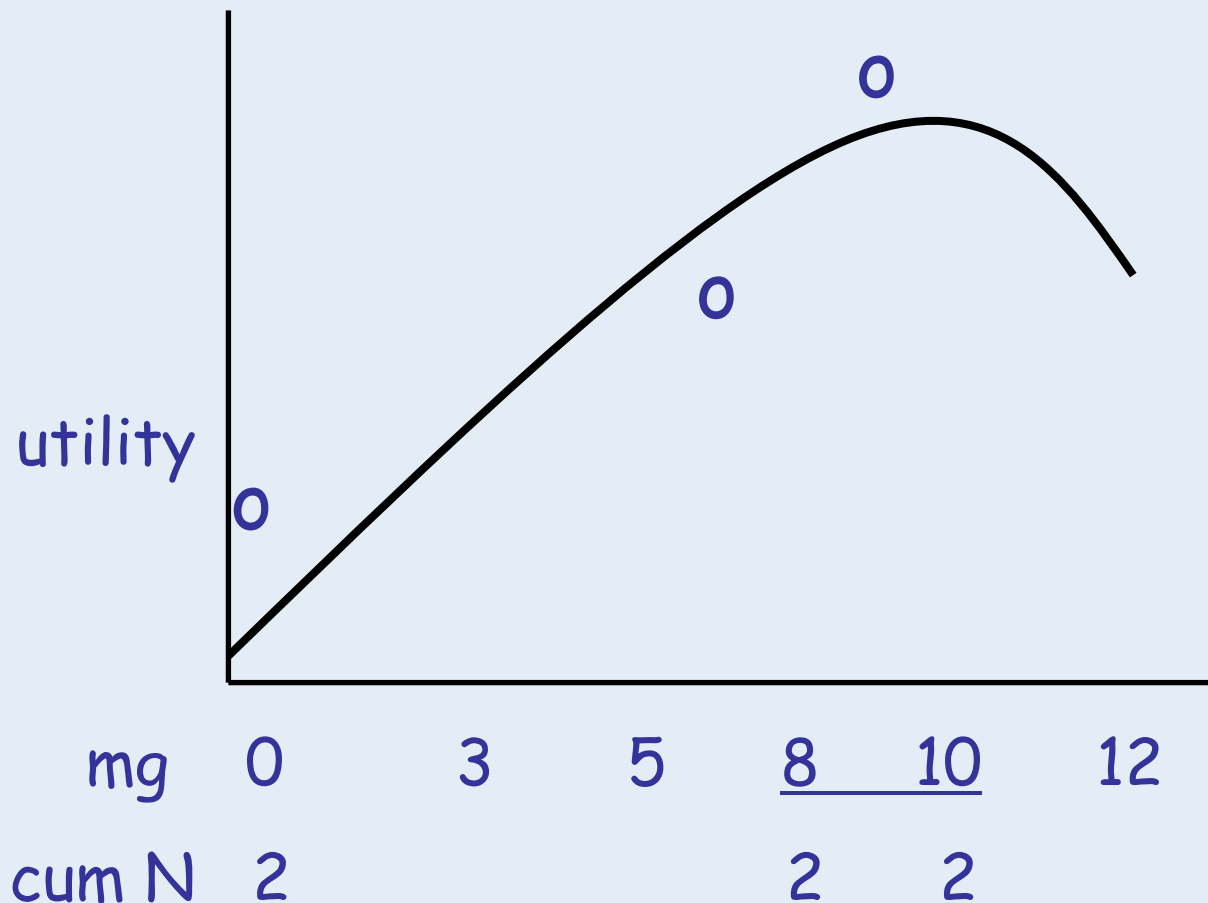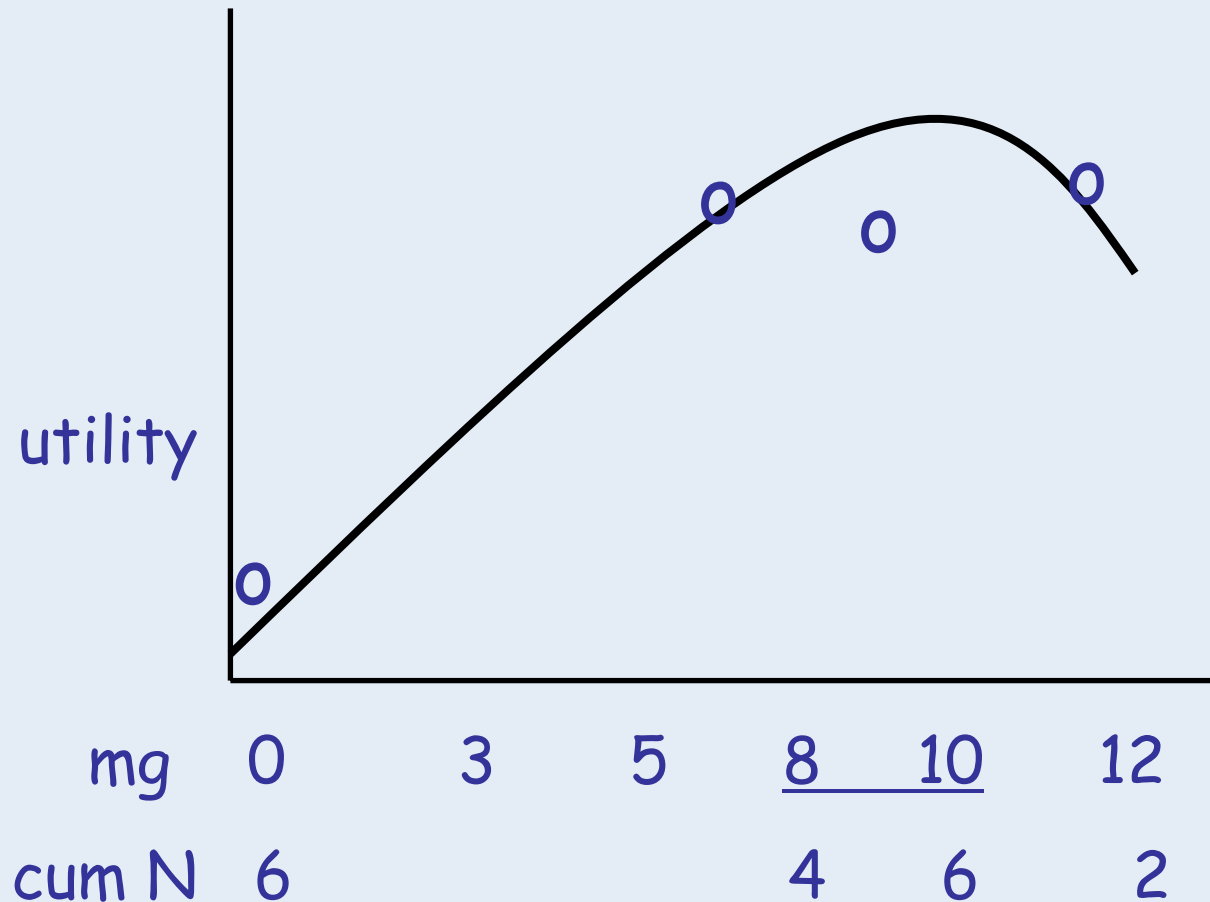


Dose response estimated using weighted quadratic regression for efficacy and isotonic regression for tolerability

| mg | 0 | 3 | 5 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|
| cum N | 2 | | | 2 | 2 | |

# "Maximizing Procedure" Example



| mg | 0 | | 3 | 5 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| cum N | 4 | | | | 2 | 4 | 2 |

# "Maximizing Procedure" Example



utility

| mg | 0 | | 3 | 5 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| cum N | 6 | | | | 4 | 6 | 2 |

# "Maximizing Procedure" Example



| mg | 0 | 3 | 5 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|
| cum N | 8 | | 2 | 6 | 6 | 2 |

# "Maximizing Procedure" Example



|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| mg | 0 | 3 | 5 | 8 | 10 | 12 |
| cum N | 10 |  | 2 | 8 | 8 | 2 |

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# "Maximizing Procedure" Example



| mg | 0 | | 3 | 5 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| cum N | 12 | | | 2 | 8 | 10 | 4 |

# "Maximizing Procedure" Example



utility

mode dose

top 2 dose

| mg | 0 | | 3 | 5 | 8 | 10 | 12 |
|---|---|---|---|---|---|---|---|
| cum N | 14 | | | 2 | 8 | 12 | 7 |

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AN
1

**8**
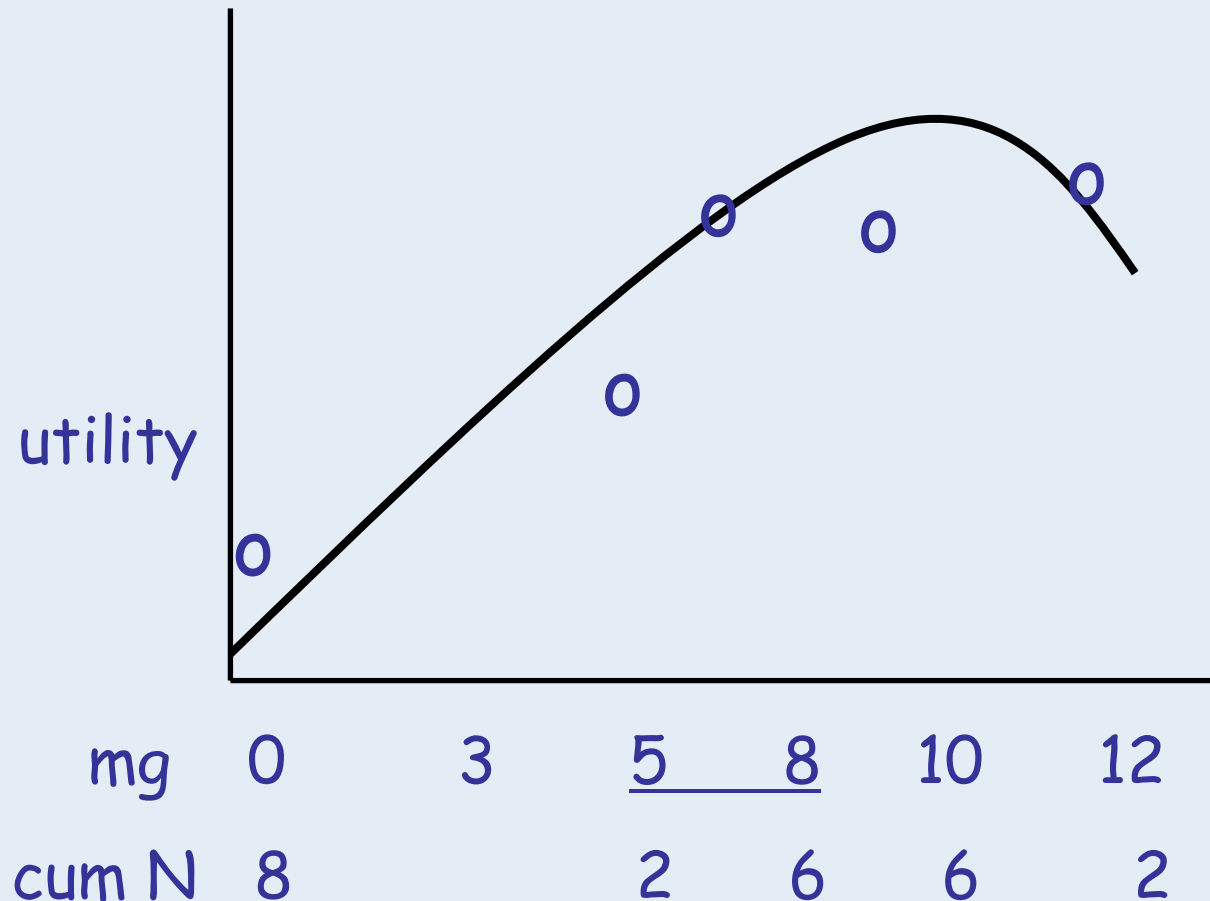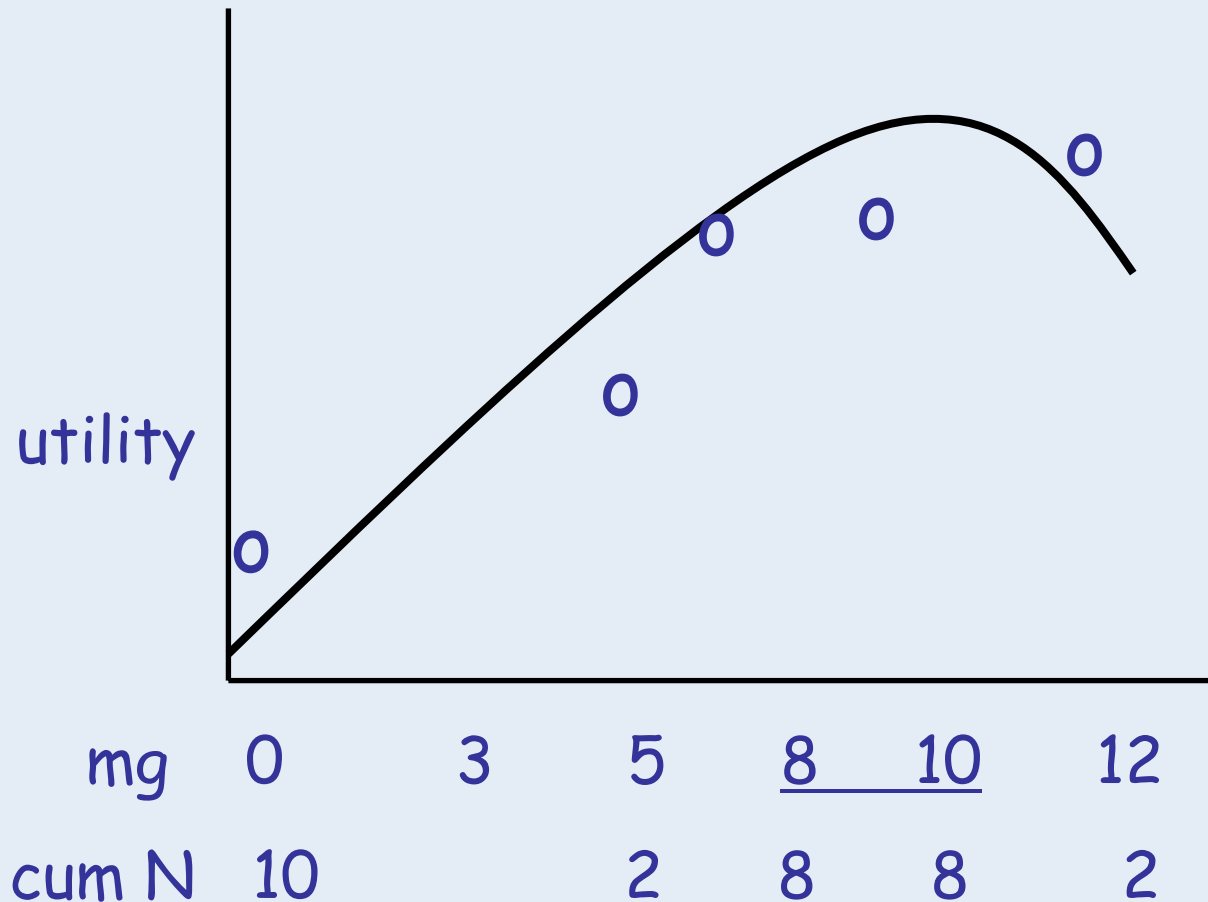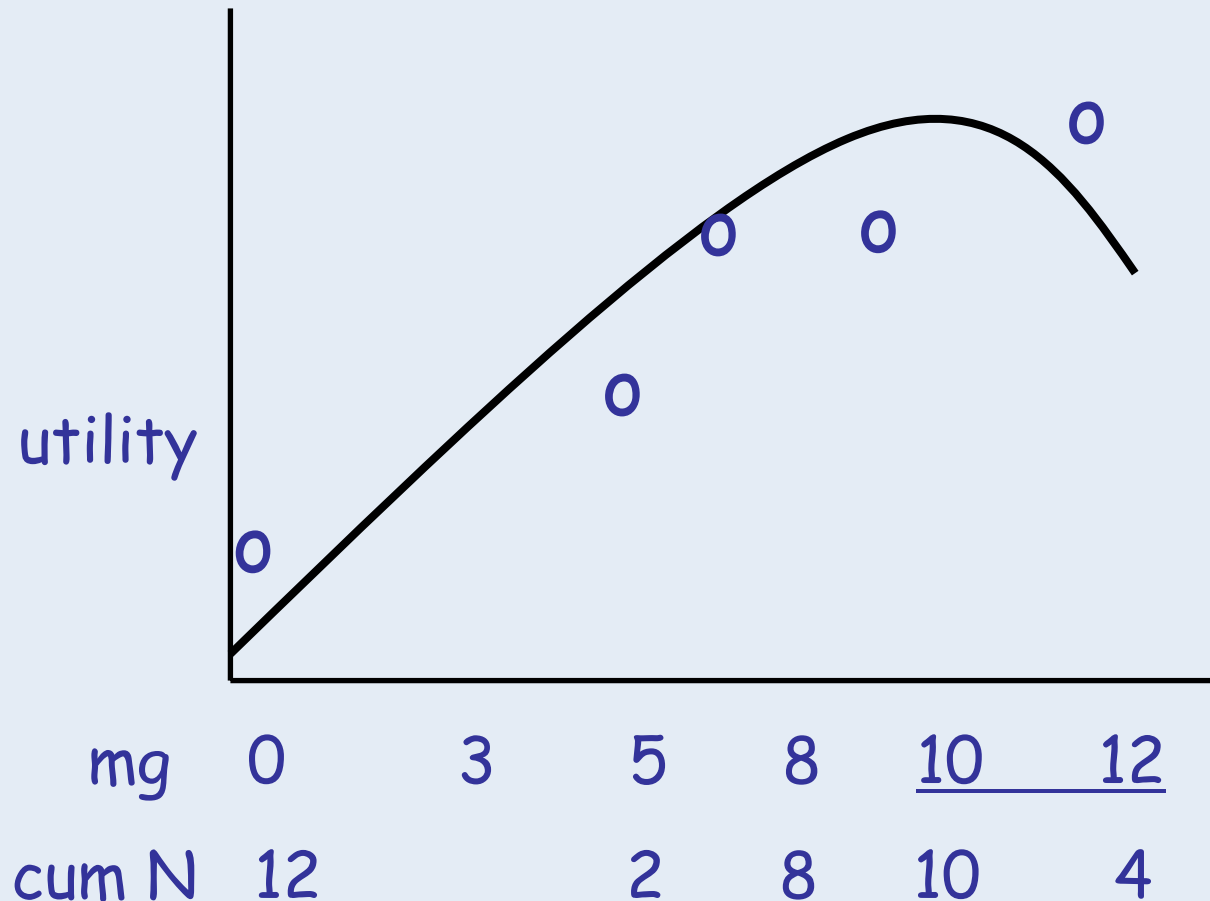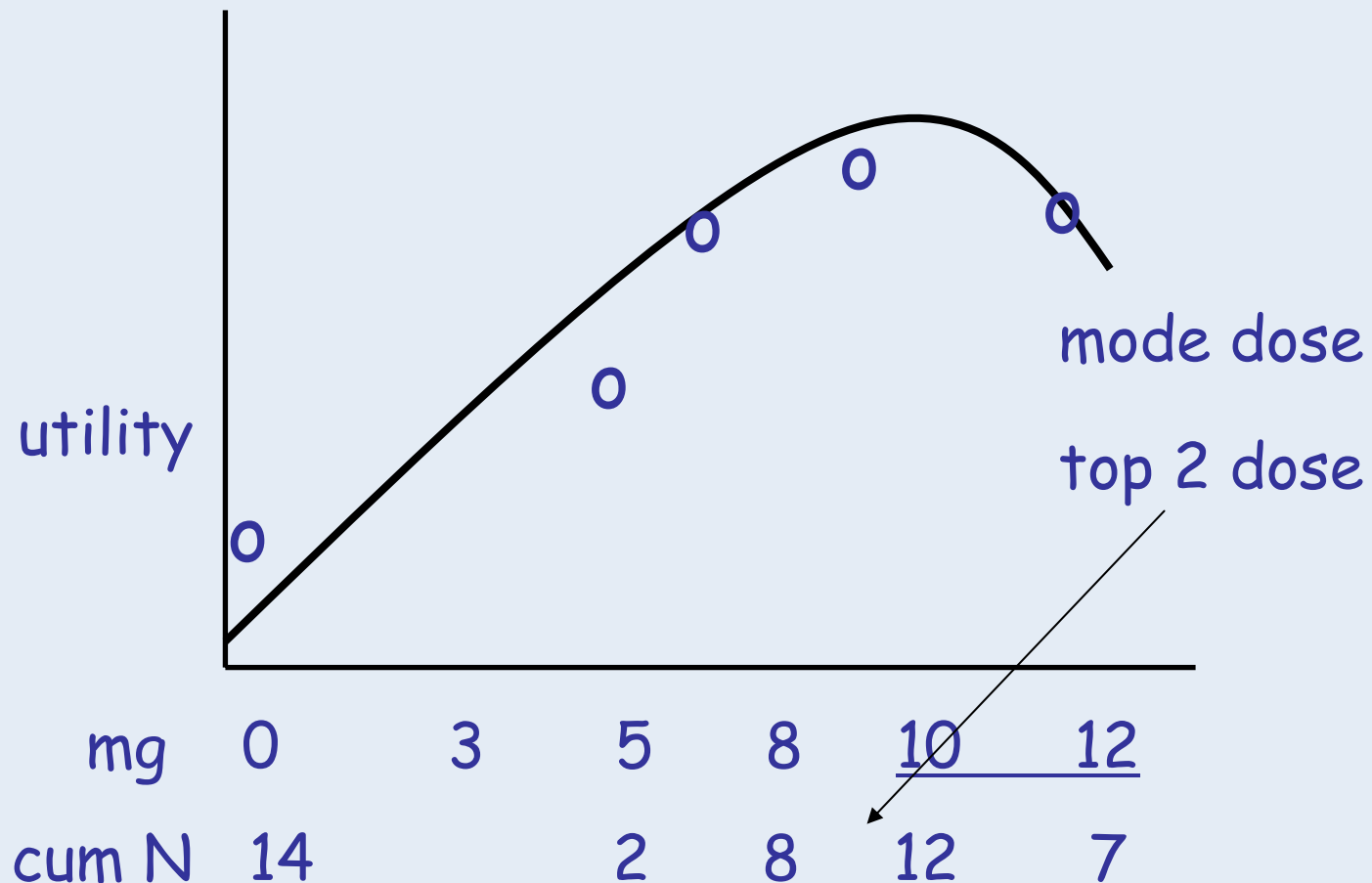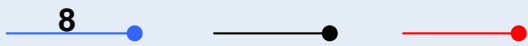
Example of Patient
Enrollment Chart
with Maximizing Procedure
Implementation

Study begins with assignment to 8 and 10 mg doses for MK dosing periods:

- first patient is randomized as noted above
- each line represents a two-week treatment period and space between lines represents a one-week washout

MK
Placebo
Active Control

Wk:  0    2    4    6    8    10   12   14   16   18   20   22  …

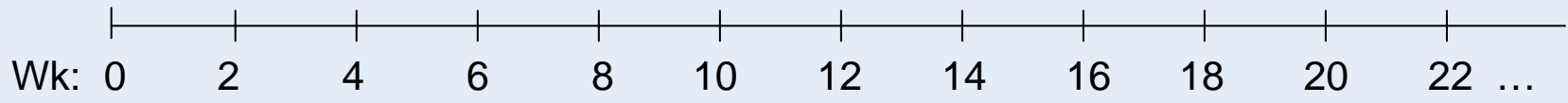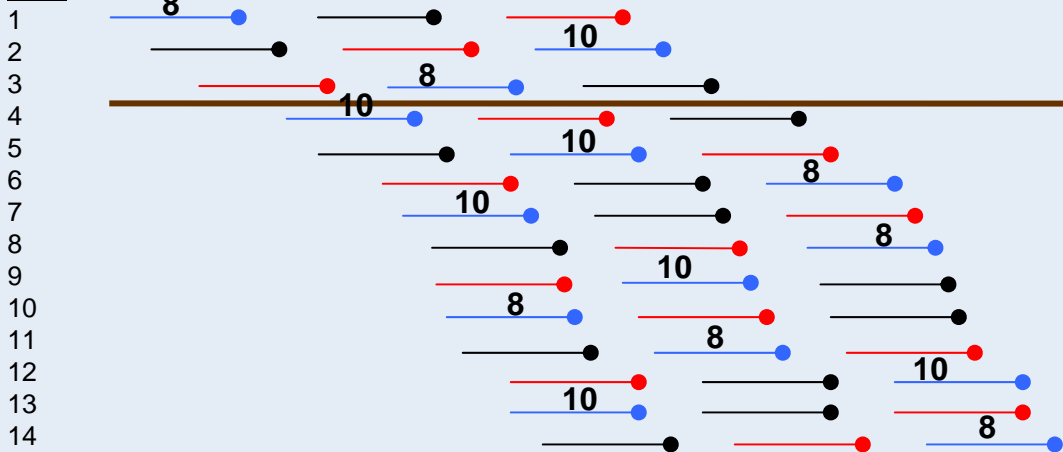Example of Patient
Enrollment Chart
with Maximizing Procedure
Implementation

**MK** (blue)
Placebo (black)
Active Control (red)

Enrollment continues over time, for example:

- 5 patients in first month
- 10 patients in second month
- 15 patients in subsequent months
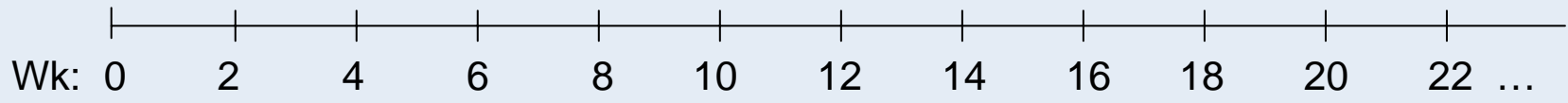
Wk: 0  2  4  6  8  10  12  14  16  18  20  22 …

Example of Patient Enrollment Chart with Maximizing Procedure Implementation
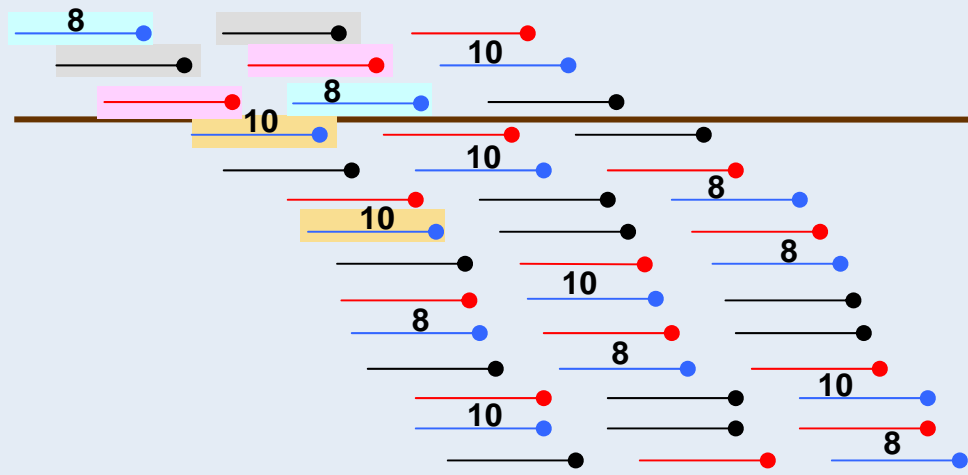
When we have 2 patients' worth of information on placebo, active control and each dose of MK, we perform the first adaptive evaluation.
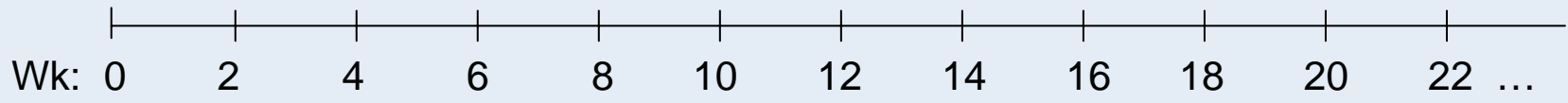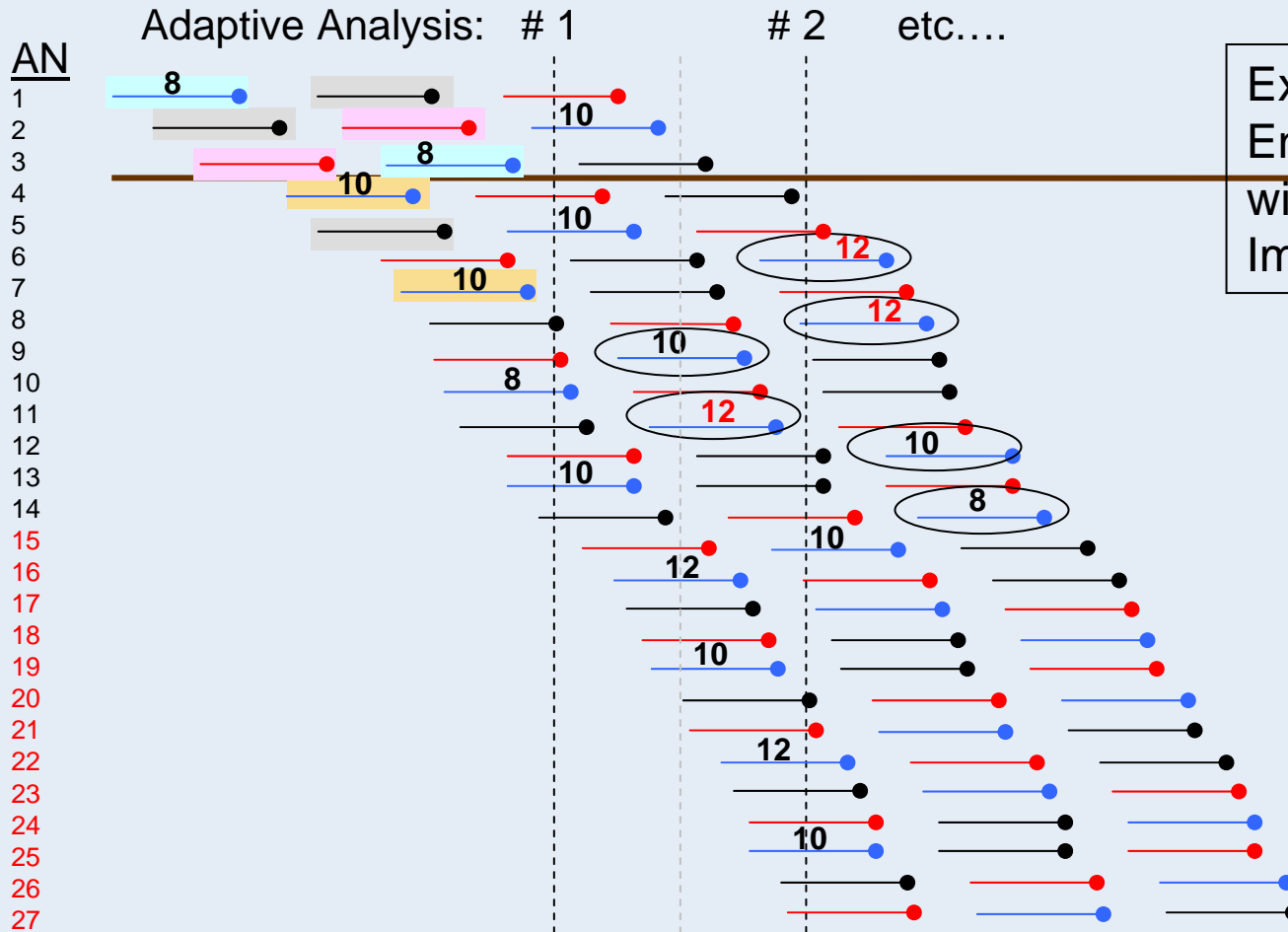
MK
Placebo
Active Control

Wk: 0    2    4    6    8    10    12    14    16    18    20    22 …

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Example of Patient Enrollment Chart with Maximizing Procedure Implementation

Adaptive Analysis: # 1    # 2    etc....

MK

Placebo

Active Control

Subsequent adaptive analyses will be conducted bi-weekly if at least two new periods of information are available on the new MK doses.
Dose assignment for MK periods will be assigned "just-in-time".

# Utility Function

$$U_d = U\left(\Delta_d, \delta_d\right) = \Delta_d - \frac{\delta_d}{10}$$

$\Delta_d$=Efficacy: MK – Active Control

$\delta_d$=Tolerability composite of (Events of Clinical Interest,
          Drug Rel Discon, Drug Rel SAE):
     MK - placebo

$d \in 5$ MK doses

# Utility Function

| Efficacy vs. Active Control | AE % vs. PBO | | | | |
|---|---|---|---|---|---|
| | 0 | 10 | 20 | 30 | 40 |
| -3 | -3 | -4 | -5 | -6 | -7 |
| -2 | -2 | -3 | -4 | -5 | -6 |
| -1 | -1 | -2 | -3 | -4 | -5 |
| 0 | 0 | -1 | -2 | -3 | -4 |
| 1 | 1 | 0 | -1 | -2 | -3 |
| 2 | 2 | 1 | 0 | -1 | -2 |
| 3 | 3 | 2 | 1 | 0 | -1 |

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# MCAR Mechanism

- $\Pr(R_2=1|Y_1,Y_2,Y_3,X) = \Pr(R_2=1|X)$
- R is a response indicator
- Y is a response

# MCAR Mechanism

- $Pr(R_2=1|Y_1,Y_2,Y_3,X) = Pr(R_2=1|X)$
- observed data are a random sample of the complete data

- period 1-3 data are MCAR x%
- x=0%, 15%, 30%

# MAR Mechanism

- $Pr(R_2=1|Y_1,Y_2,Y_3,X) = Pr(R_2=1|Y_1,X)$

# MAR Mechanism

Period 1

x%

Period 2

if Pd1 < cutpt or miss

3x%

if Pd1 >= cutpt

x/3%

Period 3

if Pd2 < cutpt or miss

3x%

if Pd2 >= cutpt

x/3%

if Pd2 < cutpt or miss

3x%

if Pd2 >= cutpt

x/3%

# NMAR Mechanism

- $Pr(R_2=1|Y_1,Y_2,Y_3,X)$ depends on $Y_2$
- $Y_2$ is missing

# NMAR Mechanism

25%  cutpoint 75%

25%(3x)+ 75%(x/3)=x

3x miss          x/3 miss

Probability Density

Efficacy        Placebo      Dose 1  ... Dose 5
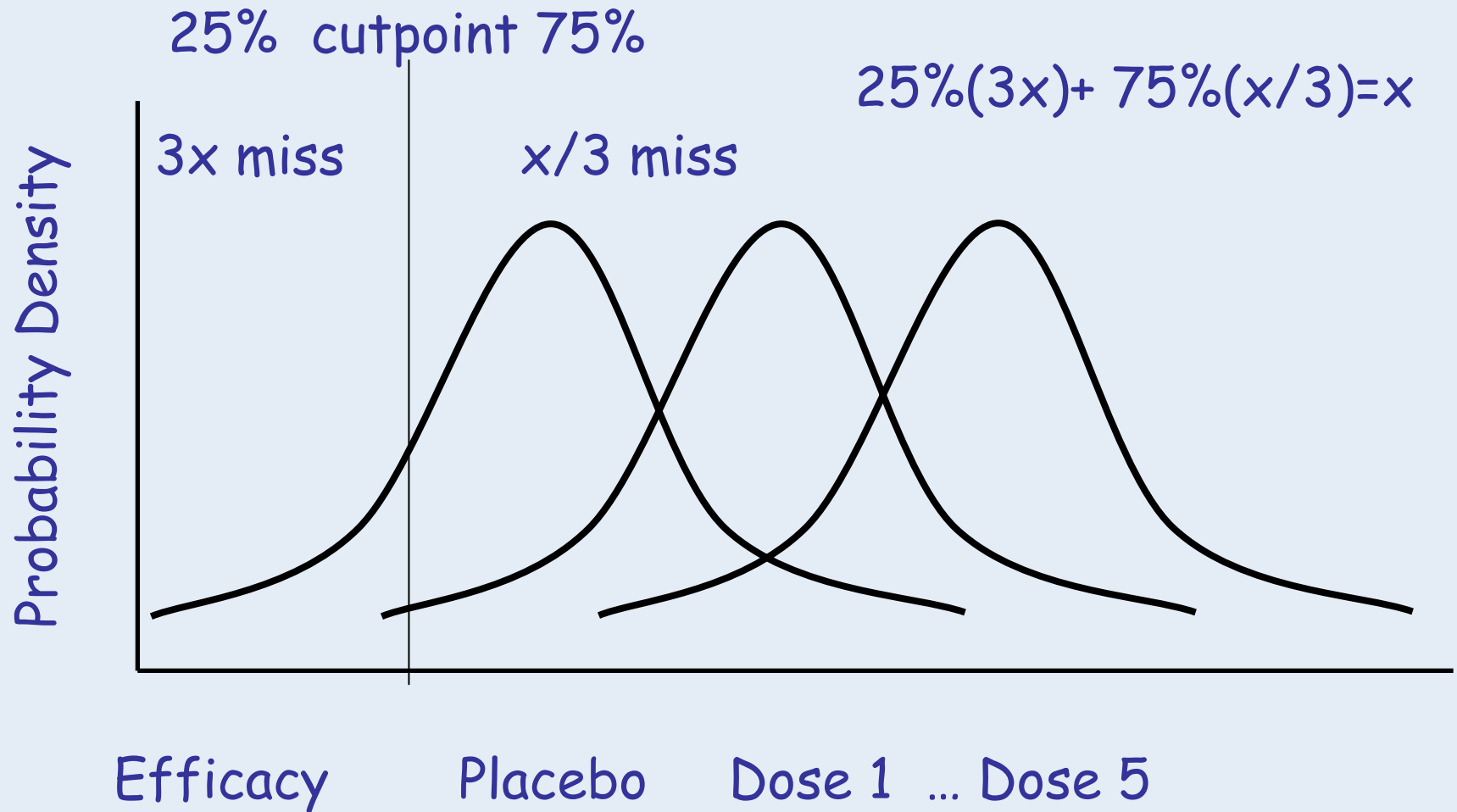
# Mixture Missing Mechanism

- 10% data are MCAR x%

- 40% data are MAR x%

- 50% data are NMAR x%


- 1/3 : 1/3 : 1/3  MCAR:MAR:NMAR

# Simulation Assumptions

- 3000 runs
- MVN(mu,sd=7)
- correlation=0.5
- 1 sided test alpha=0.025
- 7 scenarios

# Scenarios

**N Distribution**

True Utility=x
N =o

N Distribution

True Utility=x
N          =o

# N Distribution 100 Simulations

**N Distribution**

True Utility=x
N =o
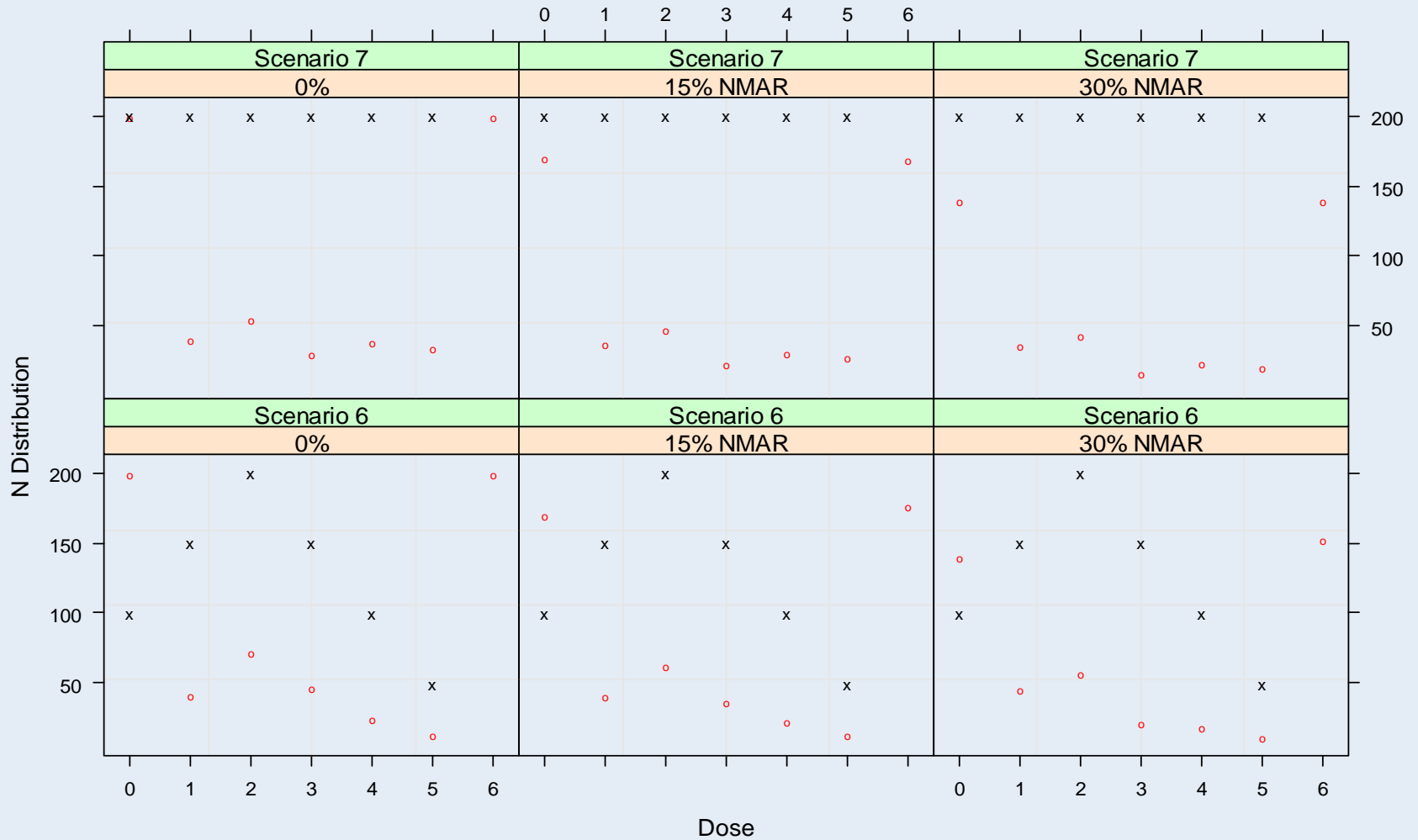
**N Distribution**

True Utility=x

N =o

# N Distribution
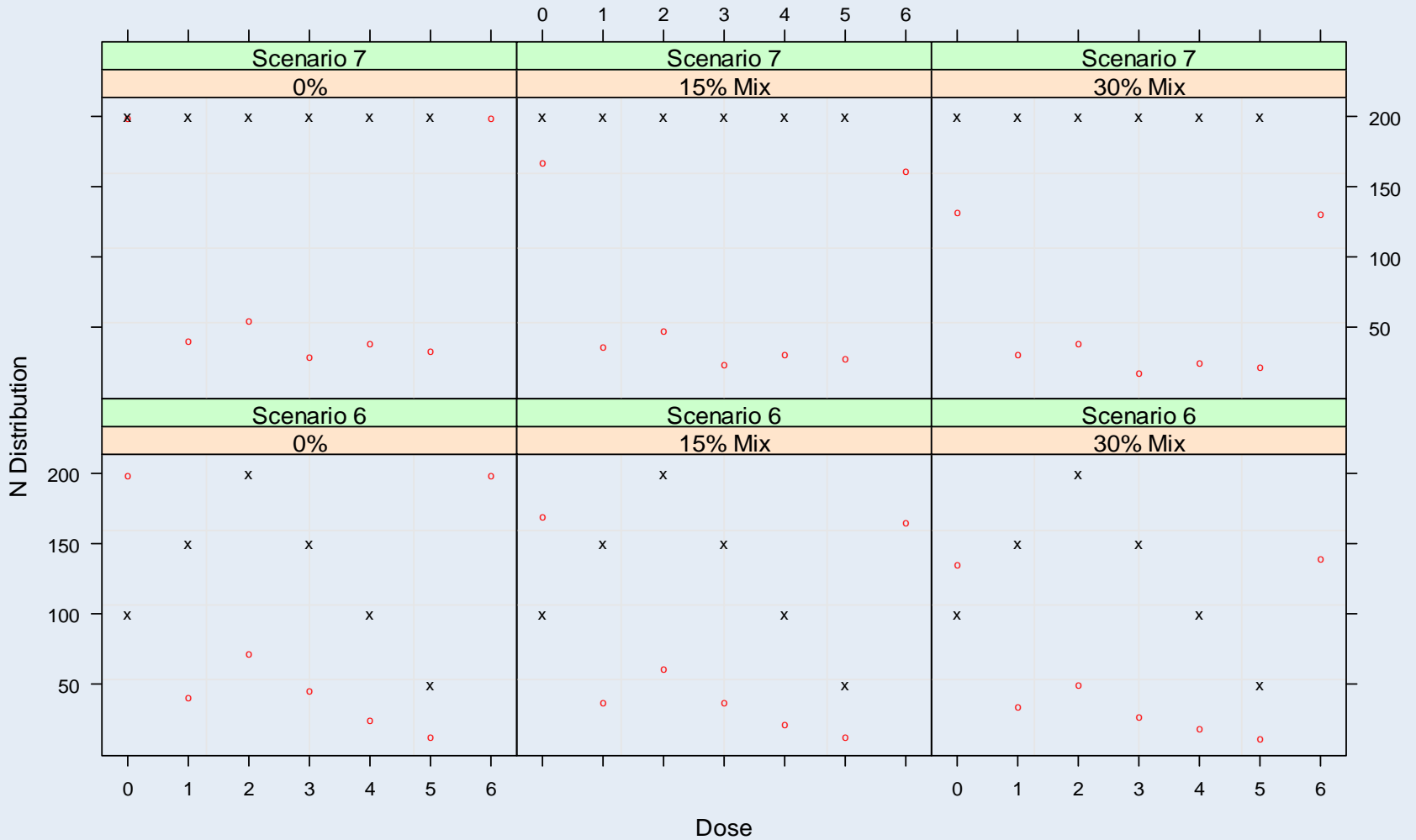
True Utility=x
N =o

N Distribution
True Utility=x
N =o
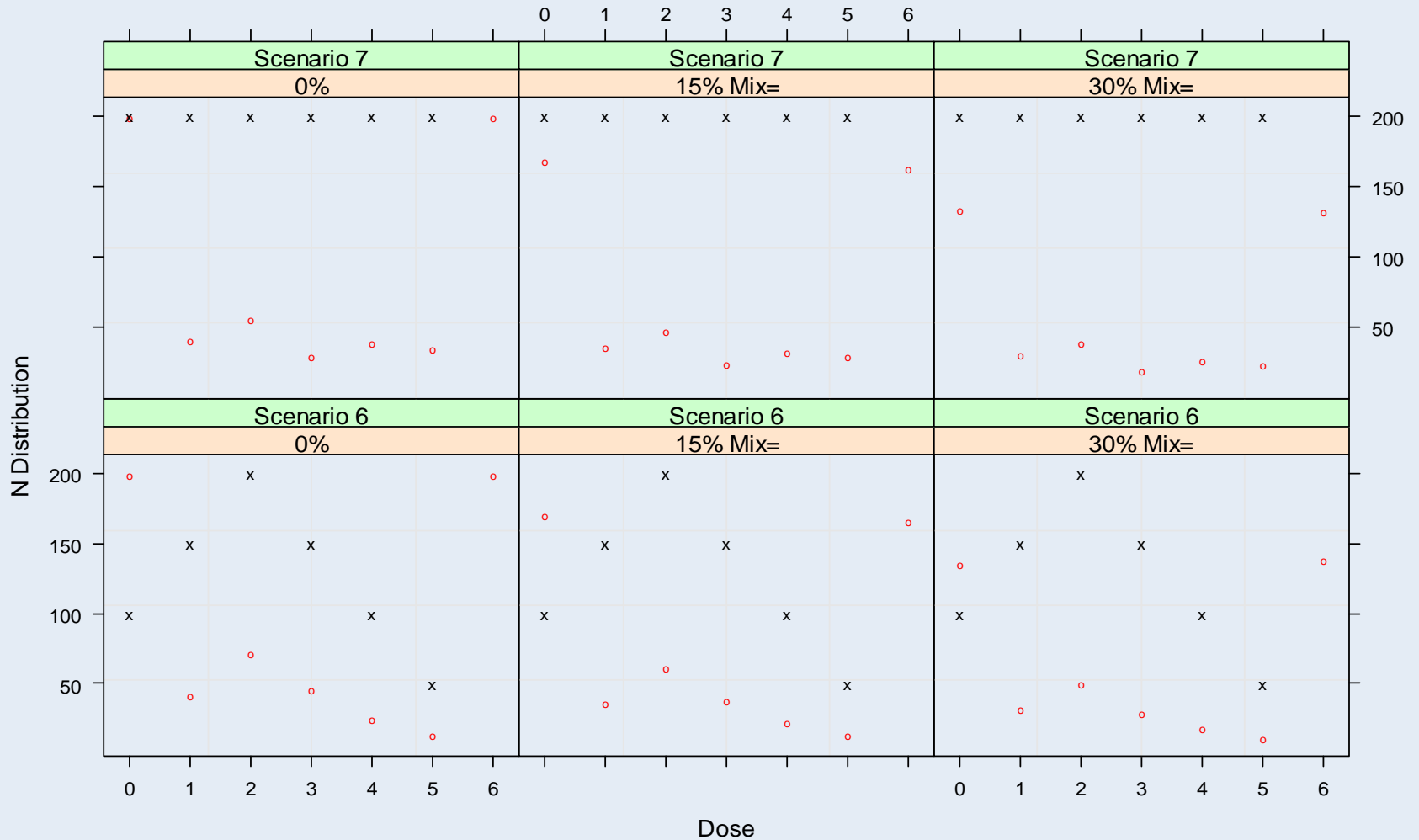
# N Distribution

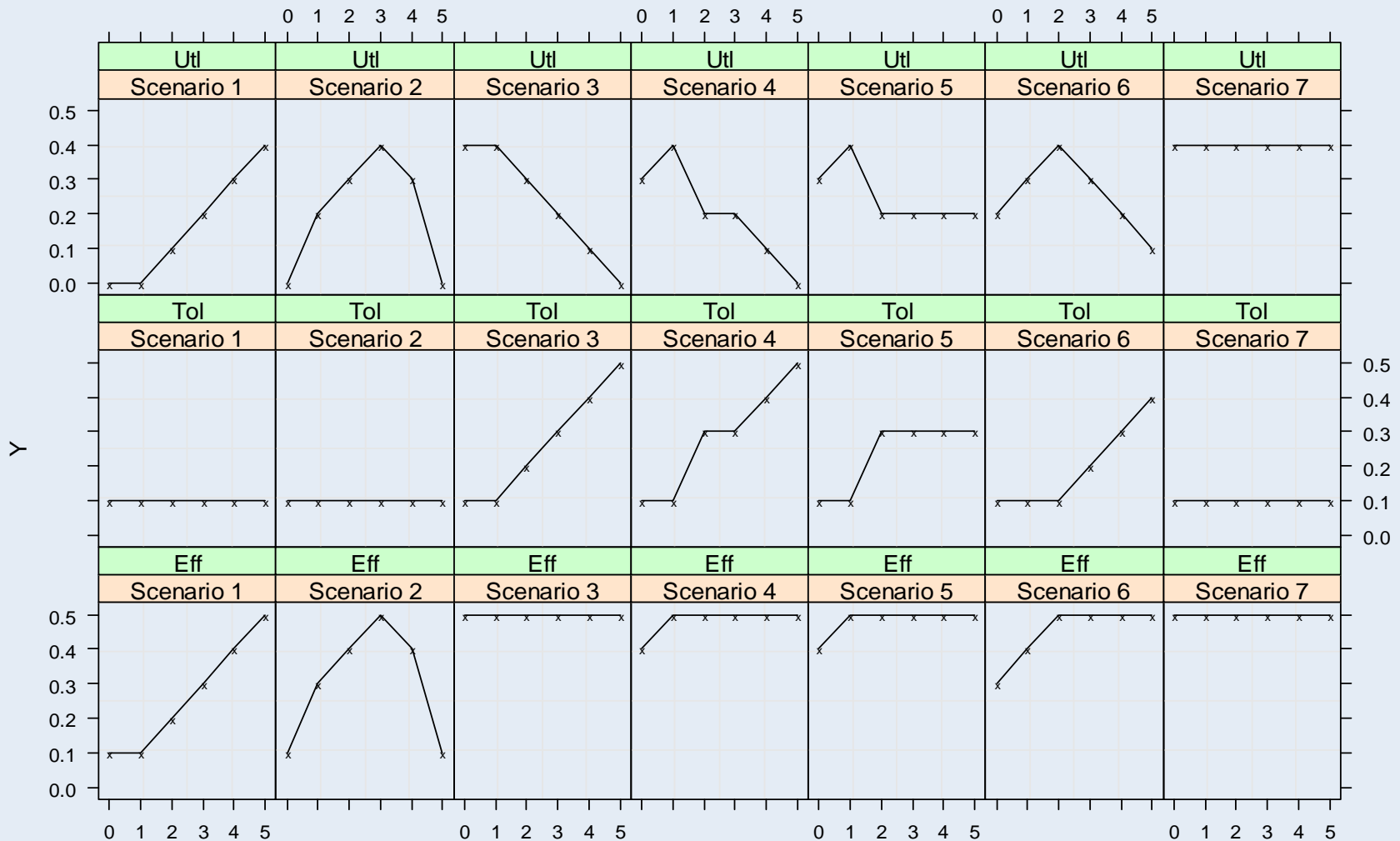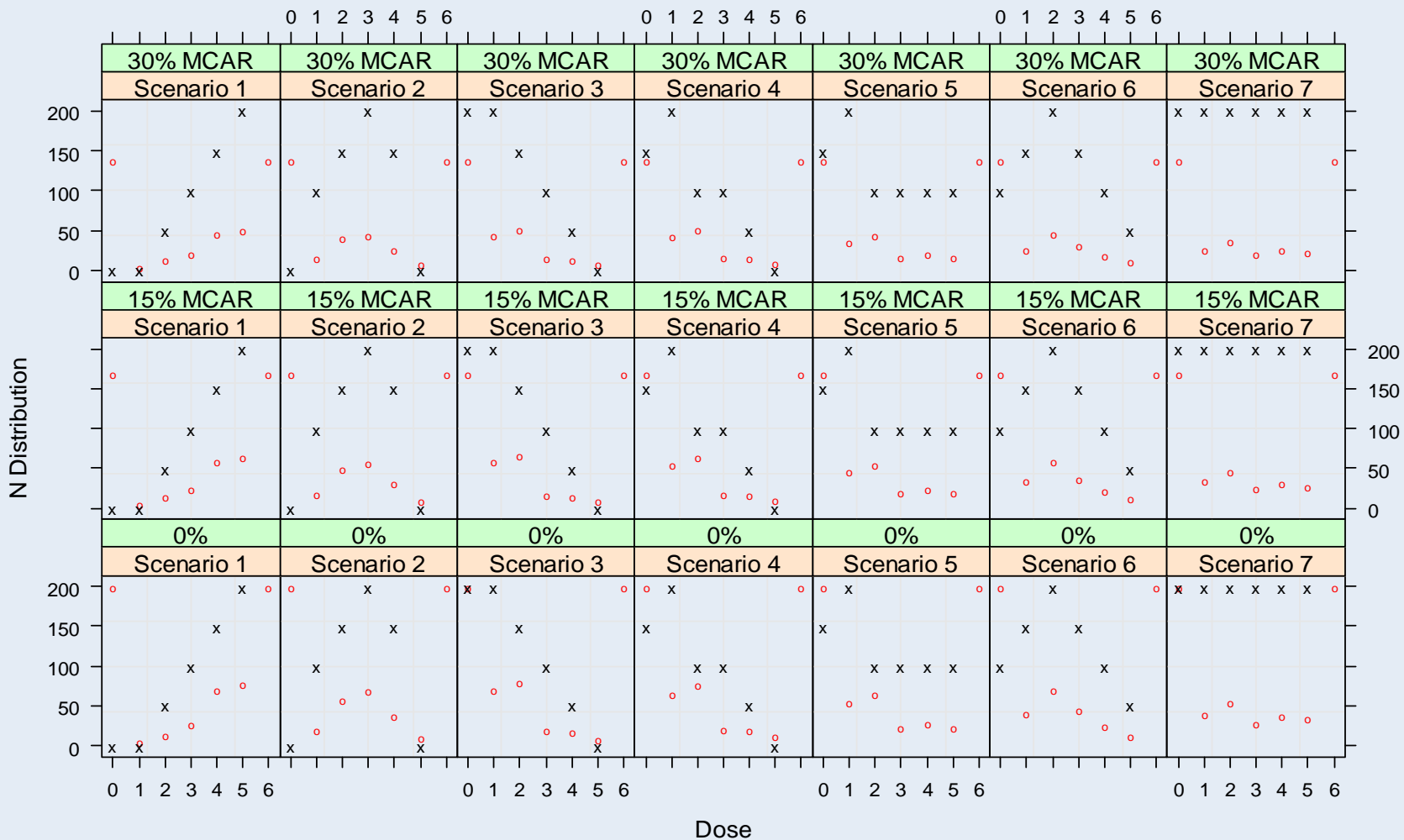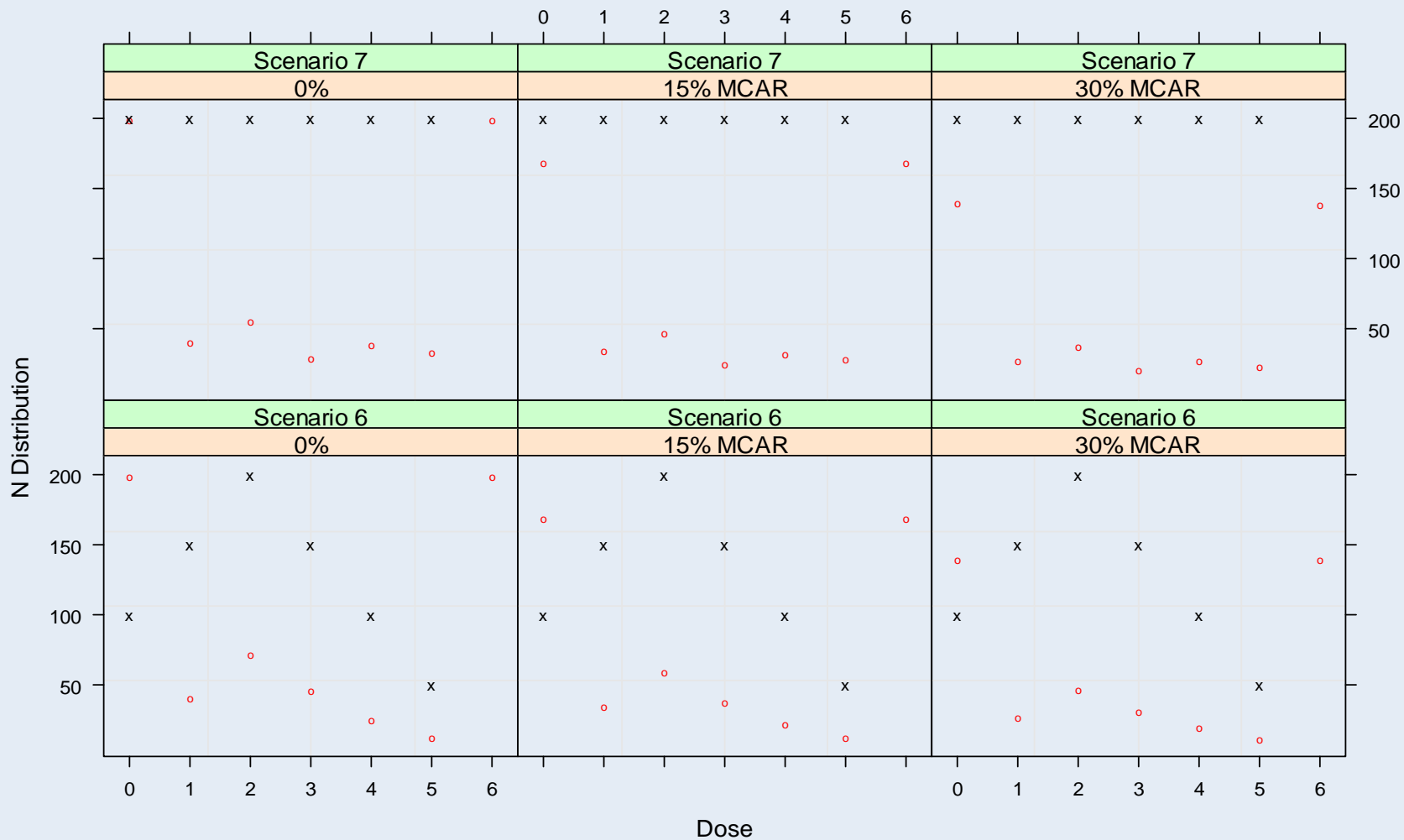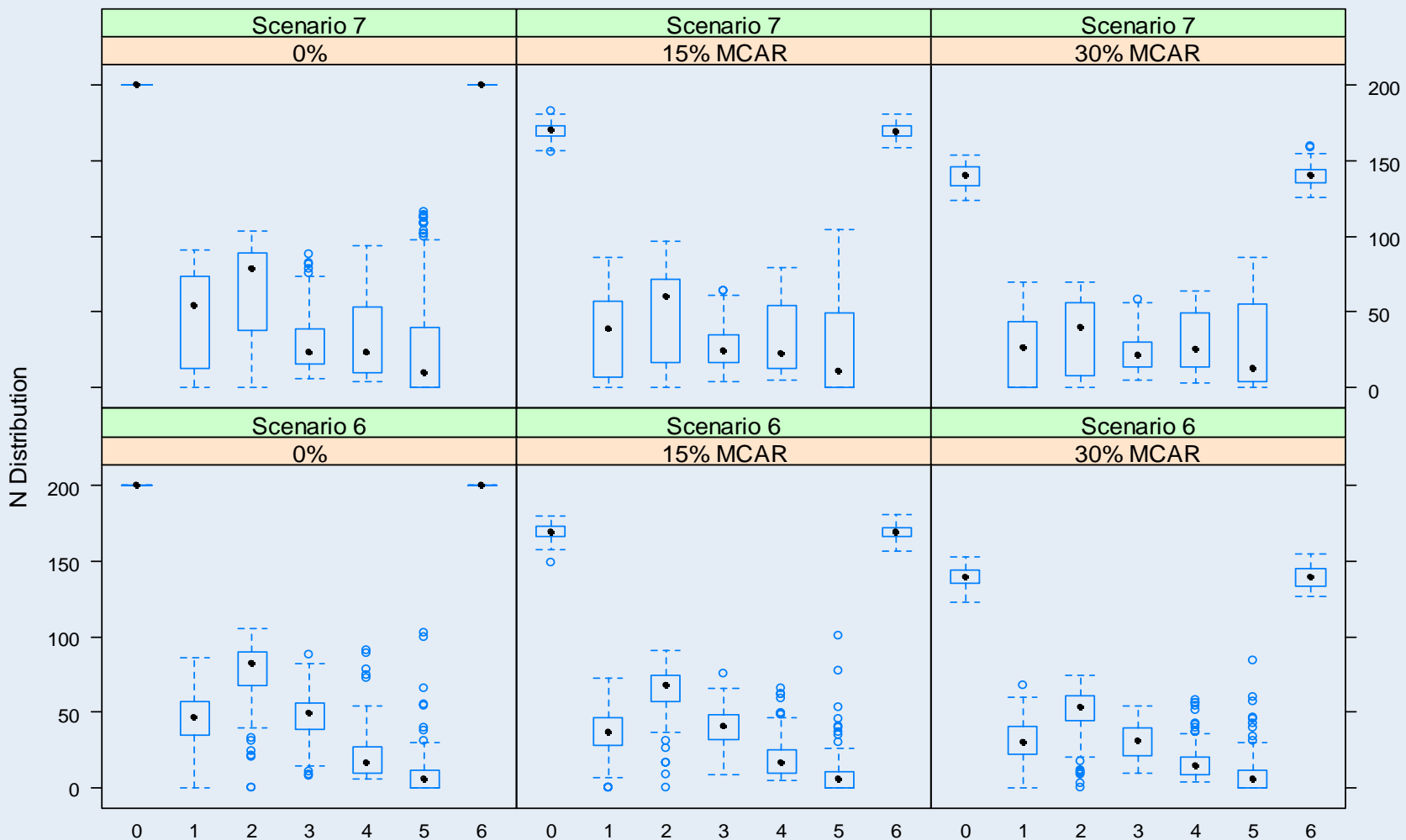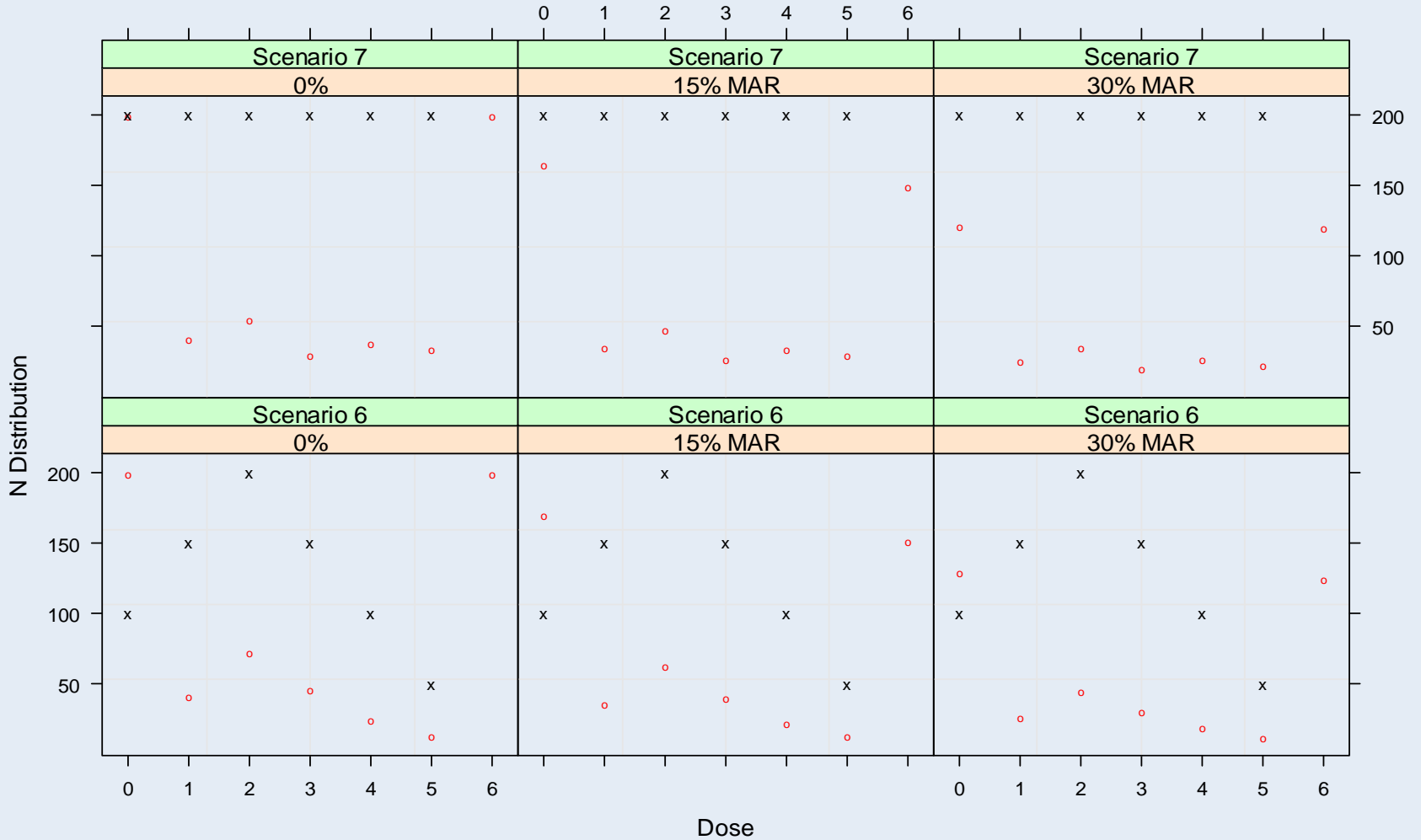| Obs | SCEN | MISS | N dose 0 | N dose 1 | N dose 2 | N dose 3 | N dose 4 | N dose 5 | N AC | MISS_PBO | MISS_MK | MISS_AC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 56 | Scenario 6 | 0% | 200 | 42 | 73 | 47 | 25 | 14 | 200 | 0.00 | 0.00 | 0.00 |
| 57 | Scenario 6 | 15% MAR | 170 | 37 | 63 | 41 | 23 | 14 | 152 | 0.15 | 0.11 | 0.24 |
| 58 | Scenario 6 | 15% MCAR | 170 | 35 | 60 | 38 | 23 | 14 | 170 | 0.15 | 0.15 | 0.15 |
| 59 | Scenario 6 | 15% Mix | 170 | 38 | 63 | 39 | 23 | 13 | 166 | 0.15 | 0.12 | 0.17 |
| 60 | Scenario 6 | 15% Mix= | 170 | 37 | 62 | 39 | 23 | 14 | 166 | 0.15 | 0.13 | 0.17 |
| 61 | Scenario 6 | 15% NMAR | 170 | 40 | 63 | 36 | 23 | 13 | 176 | 0.15 | 0.12 | 0.12 |
| 62 | Scenario 6 | 30% MAR | 130 | 27 | 46 | 31 | 20 | 12 | 125 | 0.35 | 0.32 | 0.37 |
| 63 | Scenario 6 | 30% MCAR | 140 | 28 | 48 | 32 | 20 | 12 | 140 | 0.30 | 0.30 | 0.30 |
| 64 | Scenario 6 | 30% Mix | 136 | 35 | 51 | 28 | 20 | 12 | 140 | 0.32 | 0.27 | 0.30 |
| 65 | Scenario 6 | 30% Mix= | 136 | 33 | 50 | 29 | 20 | 12 | 139 | 0.32 | 0.28 | 0.30 |
| 66 | Scenario 6 | 30% NMAR | 140 | 45 | 57 | 22 | 18 | 11 | 153 | 0.30 | 0.23 | 0.23 |
| 67 | Scenario 7 | 0% | 200 | 41 | 56 | 30 | 39 | 34 | 200 | 0.00 | 0.00 | 0.00 |
| 68 | Scenario 7 | 15% MAR | 166 | 36 | 48 | 27 | 34 | 30 | 150 | 0.17 | 0.13 | 0.25 |
| 69 | Scenario 7 | 15% MCAR | 170 | 35 | 47 | 26 | 33 | 29 | 170 | 0.15 | 0.15 | 0.15 |
| 70 | Scenario 7 | 15% Mix | 168 | 37 | 48 | 24 | 32 | 29 | 162 | 0.16 | 0.14 | 0.19 |
| 71 | Scenario 7 | 15% Mix= | 168 | 36 | 48 | 25 | 33 | 29 | 163 | 0.16 | 0.14 | 0.18 |
| 72 | Scenario 7 | 15% NMAR | 170 | 38 | 48 | 23 | 31 | 28 | 170 | 0.15 | 0.16 | 0.15 |
| 73 | Scenario 7 | 30% MAR | 122 | 26 | 36 | 21 | 27 | 23 | 121 | 0.39 | 0.34 | 0.40 |
| 74 | Scenario 7 | 30% MCAR | 140 | 28 | 38 | 22 | 28 | 24 | 140 | 0.30 | 0.30 | 0.30 |
| 75 | Scenario 7 | 30% Mix | 133 | 32 | 40 | 18 | 25 | 22 | 132 | 0.34 | 0.31 | 0.34 |
| 76 | Scenario 7 | 30% Mix= | 134 | 30 | 39 | 19 | 26 | 23 | 133 | 0.33 | 0.31 | 0.33 |
| 77 | Scenario 7 | 30% NMAR | 140 | 37 | 43 | 17 | 24 | 21 | 140 | 0.30 | 0.29 | 0.30 |

# N % Distribution

| Obs | SCEN | MISS | % pts dose 1 | % pts dose 2 | % pts dose 3 | % pts dose 4 | % pts dose 5 | MISS_PBO | MISS_MK | MISS_AC |
|---|---|---|---|---|---|---|---|---|---|---|
| 56 | Scenario 6 | 0% | 21 | 36 | 23 | 13 | 7 | 0.00 | 0.00 | 0.00 |
| 57 | Scenario 6 | 15% MAR | 21 | 36 | 23 | 13 | 8 | 0.15 | 0.11 | 0.24 |
| 58 | Scenario 6 | 15% MCAR | 21 | 35 | 23 | 14 | 8 | 0.15 | 0.15 | 0.15 |
| 59 | Scenario 6 | 15% Mix | 22 | 36 | 22 | 13 | 8 | 0.15 | 0.12 | 0.17 |
| 60 | Scenario 6 | 15% Mix= | 21 | 35 | 22 | 13 | 8 | 0.15 | 0.13 | 0.17 |
| 61 | Scenario 6 | 15% NMAR | 23 | 36 | 21 | 13 | 8 | 0.15 | 0.12 | 0.12 |
| 62 | Scenario 6 | 30% MAR | 20 | 34 | 23 | 15 | 9 | 0.35 | 0.32 | 0.37 |
| 63 | Scenario 6 | 30% MCAR | 20 | 34 | 23 | 14 | 9 | 0.30 | 0.30 | 0.30 |
| 64 | Scenario 6 | 30% Mix | 24 | 35 | 19 | 13 | 8 | 0.32 | 0.27 | 0.30 |
| 65 | Scenario 6 | 30% Mix= | 23 | 35 | 21 | 14 | 8 | 0.32 | 0.28 | 0.30 |
| 66 | Scenario 6 | 30% NMAR | 30 | 37 | 14 | 12 | 7 | 0.30 | 0.23 | 0.23 |
| | | | | | | | | | | |
| 67 | Scenario 7 | 0% | 21 | 28 | 15 | 19 | 17 | 0.00 | 0.00 | 0.00 |
| 68 | Scenario 7 | 15% MAR | 20 | 28 | 15 | 20 | 17 | 0.17 | 0.13 | 0.25 |
| 69 | Scenario 7 | 15% MCAR | 21 | 28 | 15 | 19 | 17 | 0.15 | 0.15 | 0.15 |
| 70 | Scenario 7 | 15% Mix | 22 | 28 | 14 | 19 | 17 | 0.16 | 0.14 | 0.19 |
| 71 | Scenario 7 | 15% Mix= | 21 | 28 | 15 | 19 | 17 | 0.16 | 0.14 | 0.18 |
| 72 | Scenario 7 | 15% NMAR | 23 | 29 | 14 | 19 | 17 | 0.15 | 0.16 | 0.15 |
| 73 | Scenario 7 | 30% MAR | 20 | 27 | 16 | 20 | 17 | 0.39 | 0.34 | 0.40 |
| 74 | Scenario 7 | 30% MCAR | 20 | 27 | 16 | 20 | 17 | 0.30 | 0.30 | 0.30 |
| 75 | Scenario 7 | 30% Mix | 23 | 29 | 13 | 18 | 16 | 0.34 | 0.31 | 0.34 |
| 76 | Scenario 7 | 30% Mix= | 22 | 28 | 14 | 19 | 17 | 0.33 | 0.31 | 0.33 |
| 77 | Scenario 7 | 30% NMAR | 26 | 31 | 12 | 17 | 15 | 0.30 | 0.29 | 0.30 |

N mode
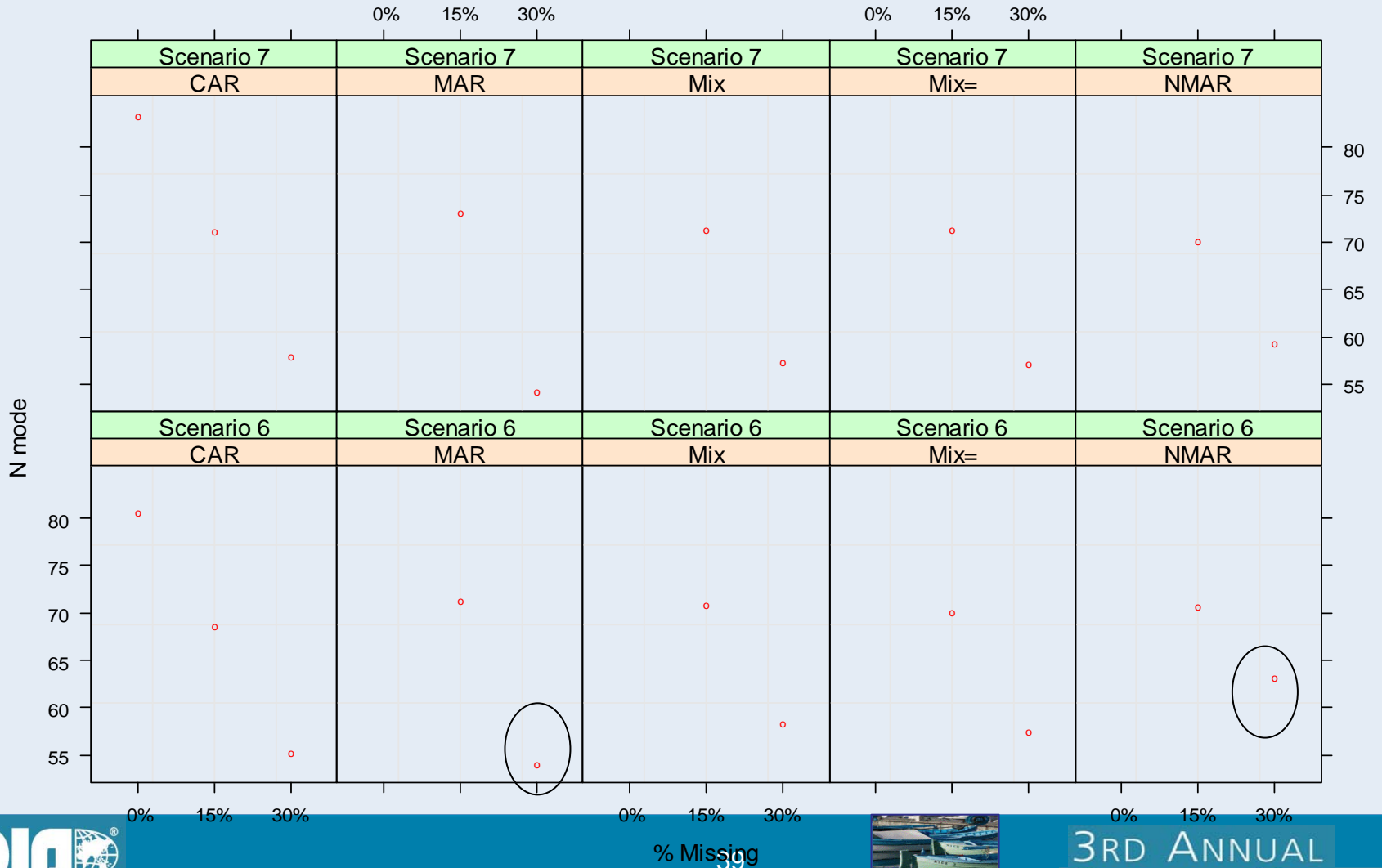
# N Mode

```
----------------------------------------------------------------------------------------
                                         SCEN
       -------------------------------------------------------------------------------
       Scenario 1    Scenario 2    Scenario 3    Scenario 4    Scenario 5    Scenario 6    Scenario 7
       -------------------------------------------------------------------------------
```

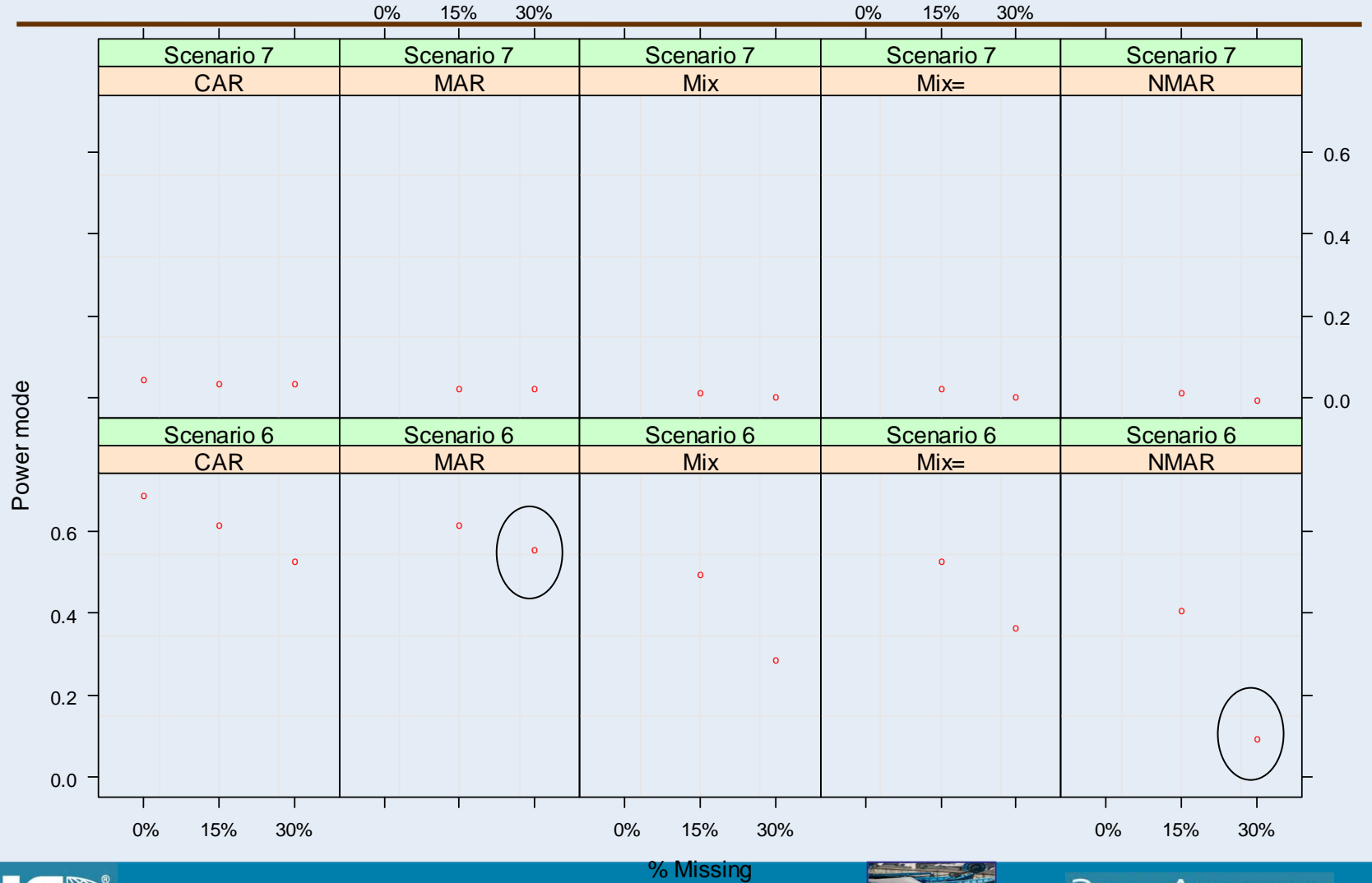| | N mode | DIFF | N mode | DIFF | N mode | DIFF | N mode | DIFF | N mode | DIFF | N mode | DIFF | N mode | DIFF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean | Mean |
| **MISS** | | | | | | | | | | | | | | |
| 0% | 92 | 0 | 79 | 0 | 86 | 0 | 85 | 0 | 85 | 0 | 81 | 0 | 83 | 0 |
| 15% MAR | 82 | 10 | 71 | 9 | 75 | 11 | 74 | 10 | 74 | 11 | 71 | 9 | 73 | 10 |
| 15% MCAR | 77 | 15 | 67 | 12 | 73 | 13 | 71 | 14 | 72 | 13 | 69 | 12 | 71 | 12 |
| 15% Mix | 81 | 11 | 70 | 10 | 73 | 13 | 74 | 11 | 74 | 11 | 71 | 10 | 71 | 12 |
| 15% Mix= | 80 | 12 | 69 | 11 | 73 | 13 | 73 | 12 | 73 | 12 | 70 | 10 | 71 | 12 |
| 15% NMAR | 82 | 10 | 70 | 10 | 71 | 15 | 73 | 12 | 73 | 12 | 71 | 10 | 70 | 13 |
| 30% MAR | 63 | 29 | 54 | 25 | 55 | 31 | 55 | 30 | 56 | 29 | 54 | 27 | 54 | 29 |
| 30% MCAR | 62 | 29 | 55 | 25 | 59 | 27 | 58 | 26 | 59 | 27 | 55 | 25 | 58 | 25 |
| 30% Mix | 68 | 24 | 57 | 22 | 58 | 28 | 59 | 25 | 60 | 25 | 58 | 22 | 58 | 26 |
| 30% Mix= | 66 | 26 | 56 | 23 | 58 | 28 | 59 | 26 | 59 | 26 | 58 | 23 | 57 | 26 |
| 30% NMAR | 73 | 19 | 61 | 19 | 60 | 26 | 63 | 22 | 63 | 22 | 63 | 17 | 59 | 24 |

# Summary N Distribution

- on average, "Maximizing Procedure" allocates most patients on dose with highest utility

- MNAR mode dose has more patients than MAR

# Power Mode vs Pbo

# Power Mode Vs Placebo

```
-----------------------------------------------------------------------------------------
                                         SCEN
-----------------------------------------------------------------------------------------
       Scenario 1      Scenario 2      Scenario 3      Scenario 4      Scenario 5      Scenario 6      Scenario 7
-----------------------------------------------------------------------------------------
       Power           Power           Power           Power           Power           Power           Power
       mode            mode            mode            mode            mode            mode            mode
       vs              vs              vs              vs              vs              vs              vs
       PBO    DIFF     PBO    DIFF     PBO    DIFF     PBO    DIFF     PBO    DIFF     PBO    DIFF     PBO    DIFF
-----------------------------------------------------------------------------------------
       Mean   Mean     Mean   Mean     Mean   Mean     Mean   Mean     Mean   Mean     Mean   Mean     Mean   Mean
-----------------------------------------------------------------------------------------
MISS
-----------
0%         93     0      98     0       3     0      22     0      26     0      69     0       5     0
-----------------------------------------------------------------------------------------
15% MAR    90     3      97     1       2     1      18     4      20     6      62     7       3     2
-----------------------------------------------------------------------------------------
15% MCAR   90     3      96     2       2     1      18     4      23     3      62     7       4     1
-----------------------------------------------------------------------------------------
15% Mix    87     6      94     4       1     2      12    10      16    10      50    19       2     3
-----------------------------------------------------------------------------------------
15% Mix=   89     4      95     3       1     2      14     8      16    10      53    16       3     2
-----------------------------------------------------------------------------------------
15% NMAR   84     9      92     6       1     2       8    14      10    16      41    28       2     3
-----------------------------------------------------------------------------------------
30% MAR    87     6      92     6       2     1      16     6      20     6      56    13       3     2
-----------------------------------------------------------------------------------------
30% MCAR   84     9      92     6       2     1      18     4      19     7      53    16       4     1
-----------------------------------------------------------------------------------------
30% Mix    75    18      79    19       1     2       5    17       6    20      29    40       1     4
-----------------------------------------------------------------------------------------
30% Mix=   79    14      84    14       1     2       9    13      11    15      37    32       1     4
-----------------------------------------------------------------------------------------
30% NMAR   55    38      54    44       0     3       1    21       1    25      10    59       0     5
```
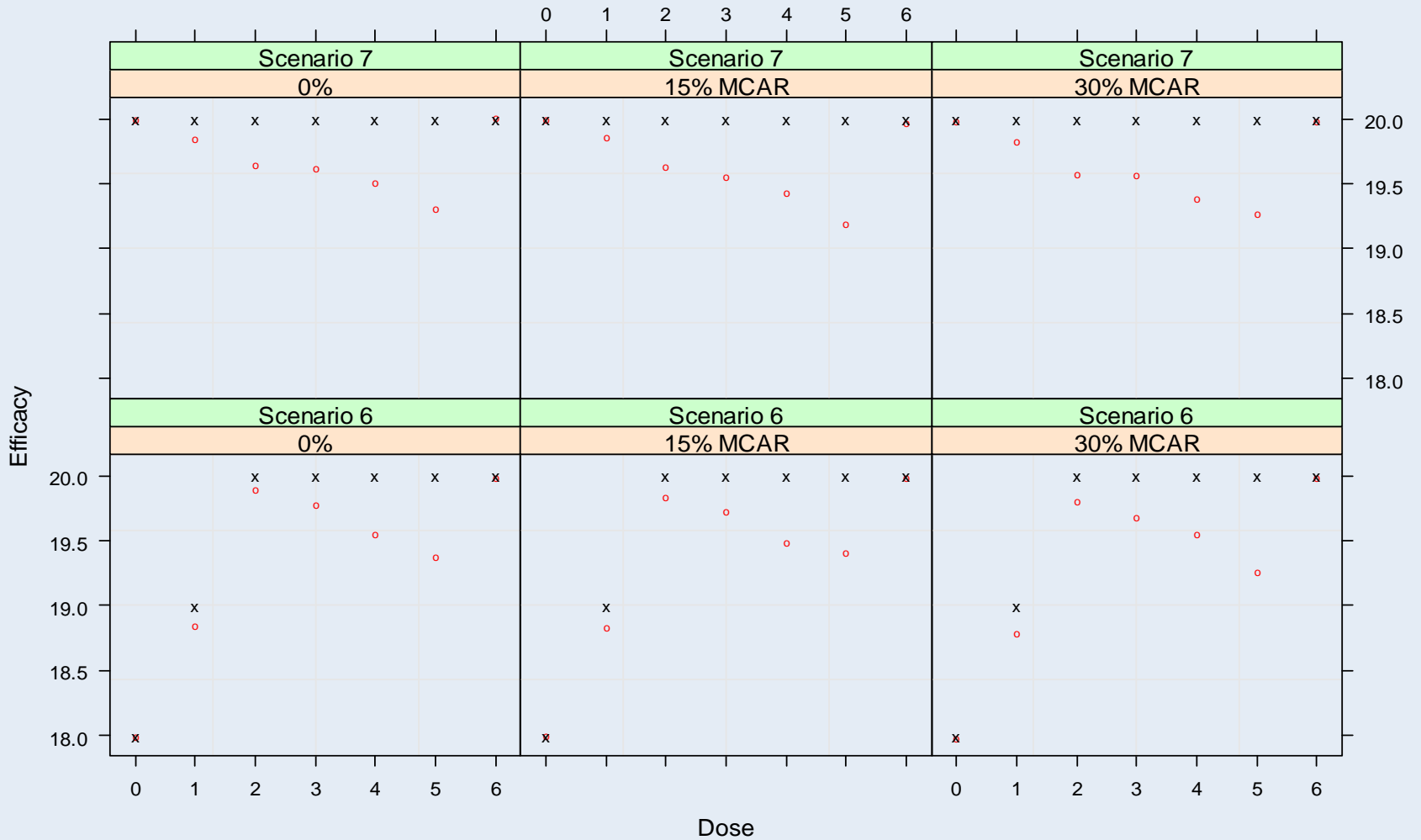
# Summary Power vs Placebo

- more missing -> lower power
- MAR has highest power (even though MNAR has bigger N)
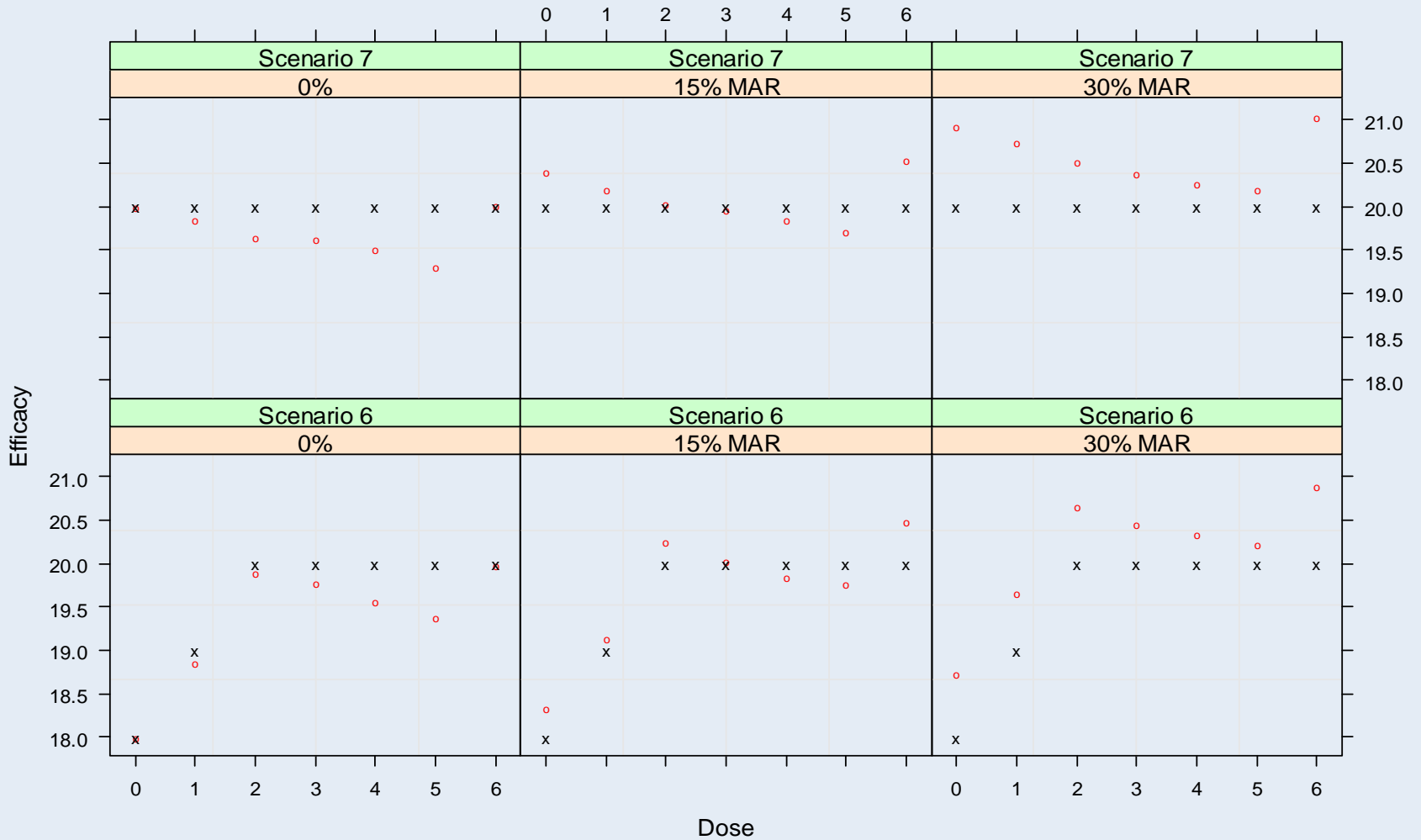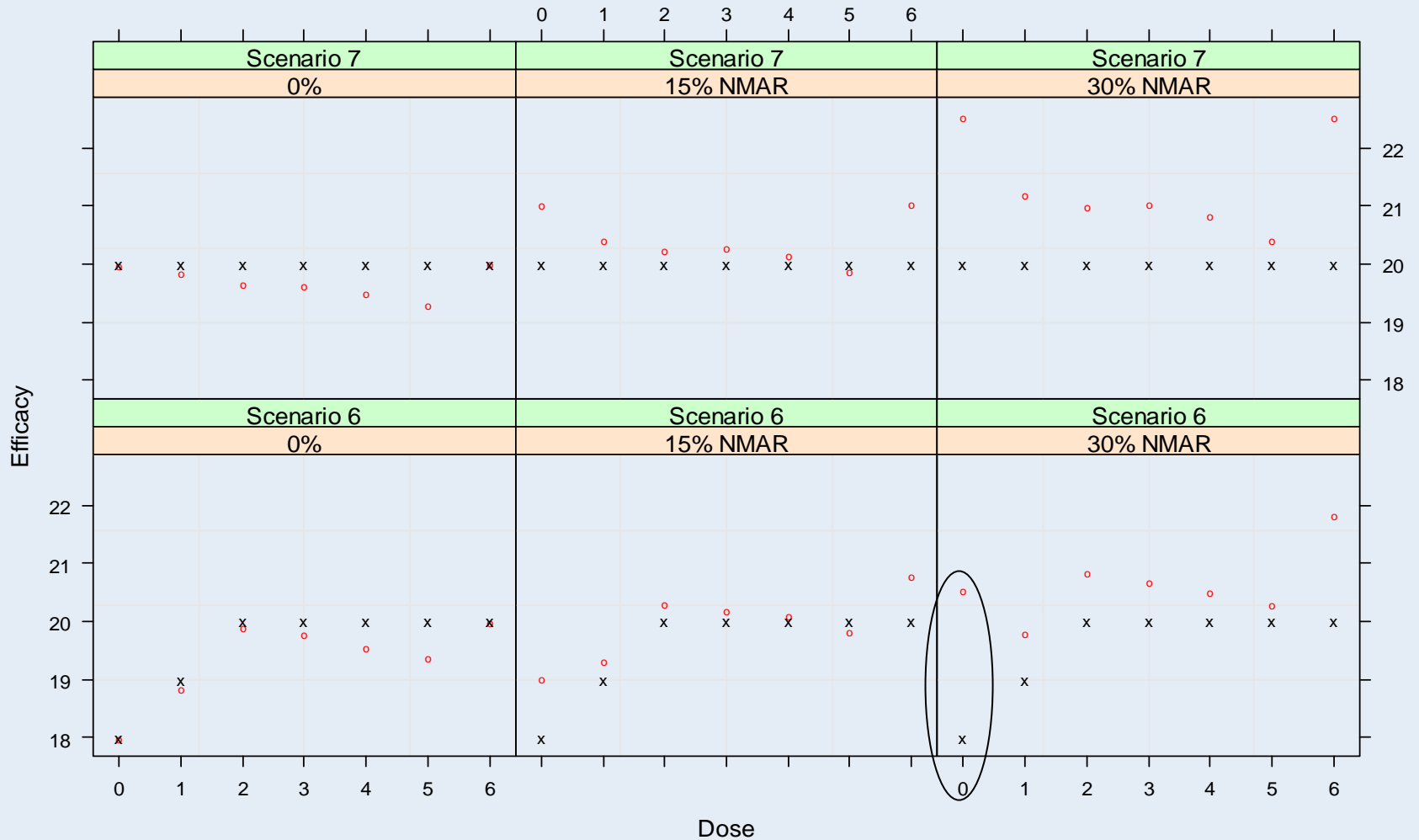
Efficacy
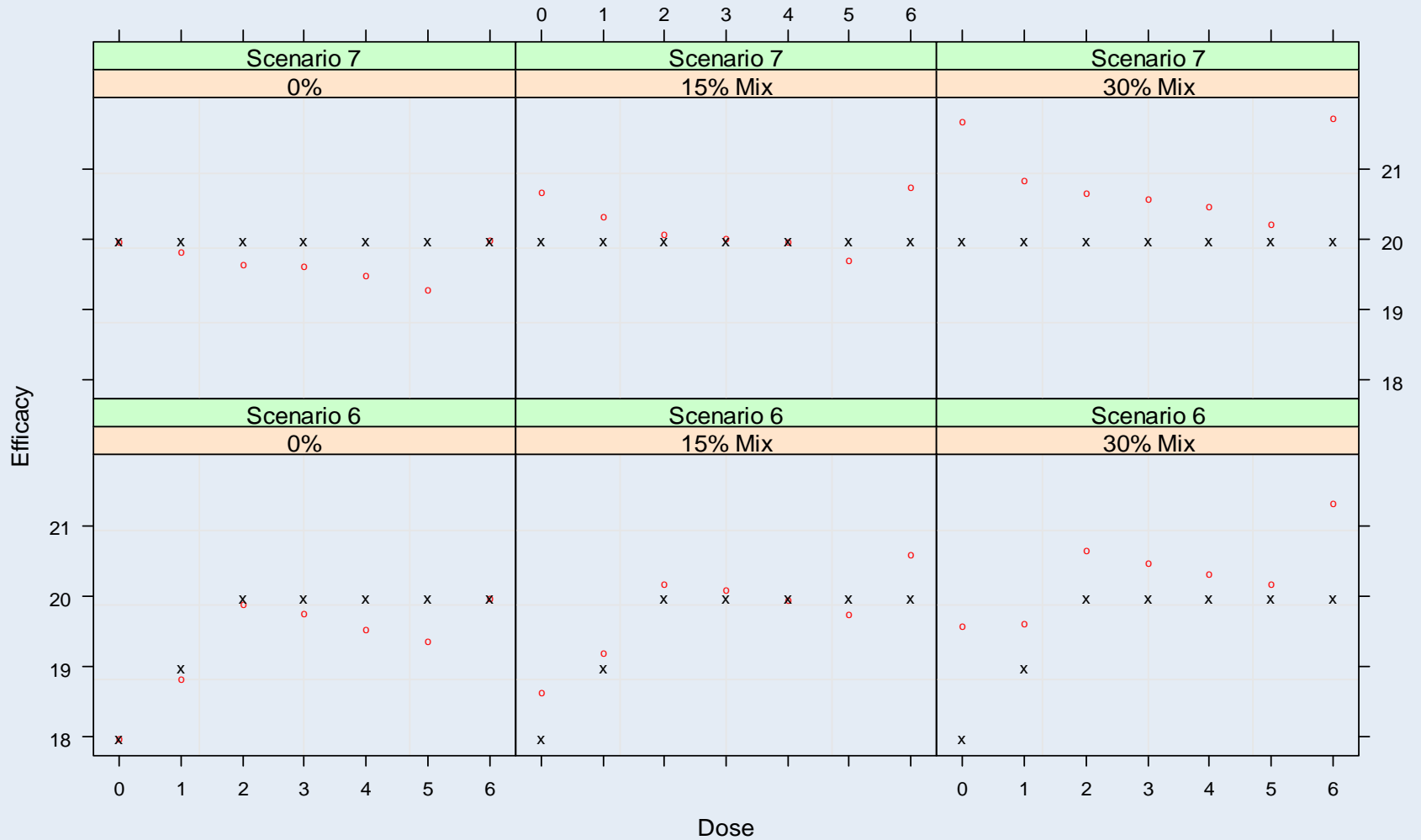
True    =x
Estimate=o

Efficacy

True =x
Estimate=o

Efficacy

True =x
Estimate=o

Efficacy
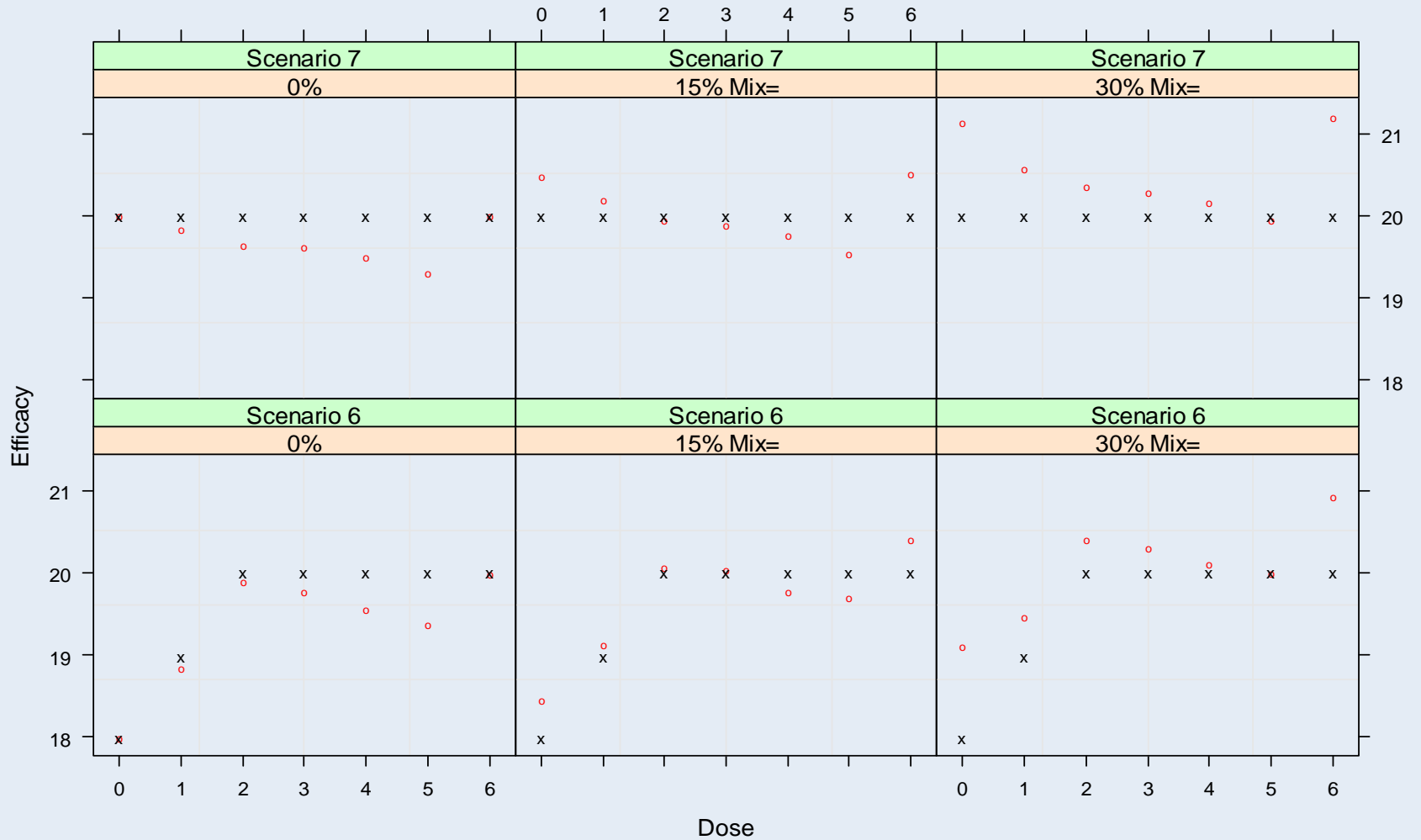
Utility
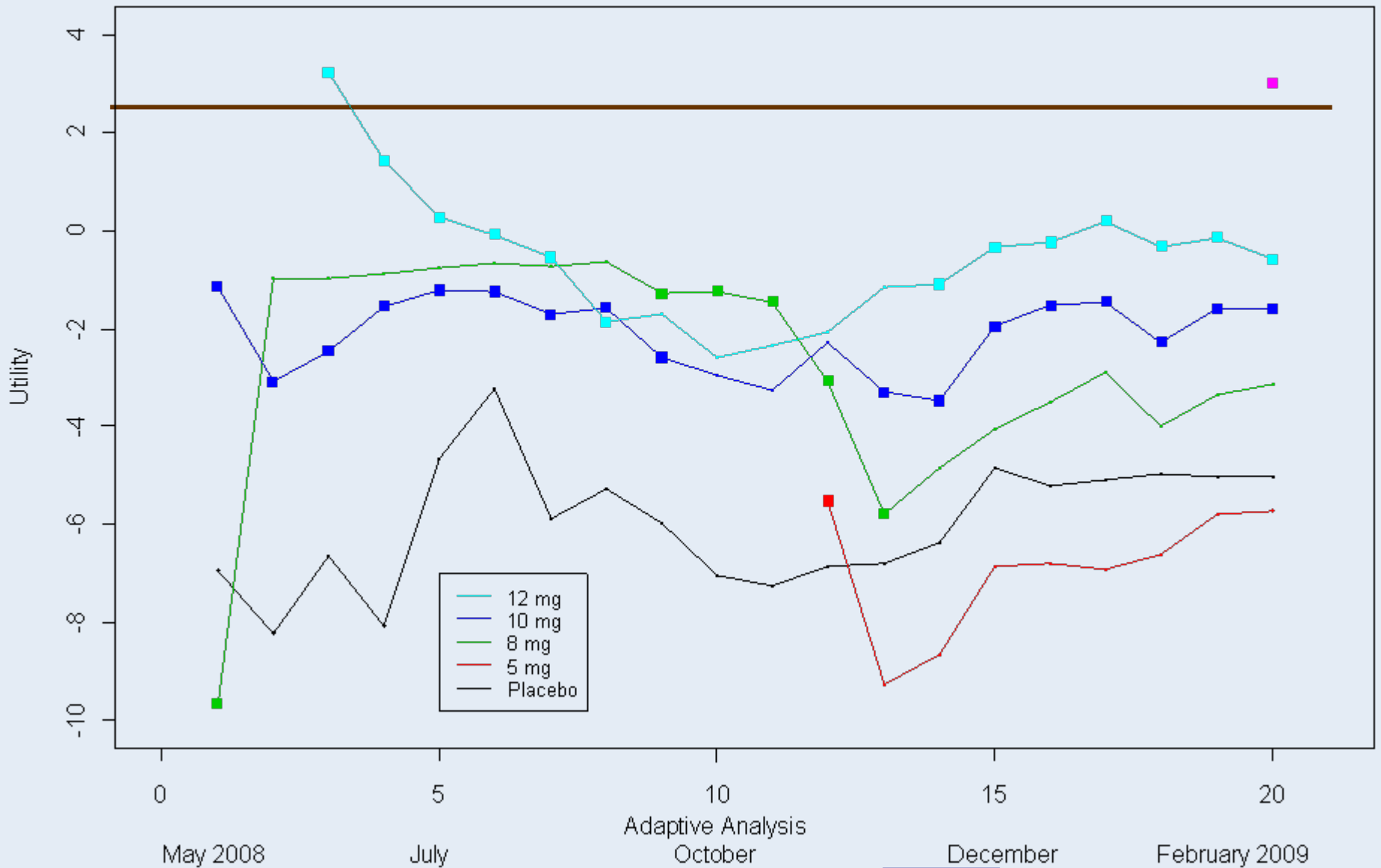
# Distribution of Patients

| Treatment | N |
|---|---|
| Placebo | 117 |
| MK   5 mg | 10 |
| MK   8 mg | 25 |
| MK 10 mg | 46 |
| MK 12 mg | 38 |
| MK (top 2 doses[‡] ) | 84 |
| Active Control | 111 |

# Study Results

| Estimated Differences | Difference in LS Means (95% CI) |
|---|---|
| MK   5 mg vs Placebo | -1 ( -6,   2) |
| MK   8 mg vs Placebo | 2 ( -1,   5) |
| MK 10 mg vs Placebo | 0 ( -2,   3) |
| MK 12 mg vs Placebo | 1 ( -1,   3) |
| MK (top 2 doses[‡] ) vs Placebo | 1 ( -1,   2) |
| Active Control vs Placebo | 4 ( 3,   6) |
| MK   5 mg vs Active Control | -6 (-10, -2) |
| MK   8 mg vs Active Control | -3 ( -5,   0) |
| MK 10 mg vs Active Control | -4 ( -6, -2) |
| MK 12 mg vs Active Control | -3 ( -6, -1) |
| MK (top 2 doses[‡] ) vs Active Control | -4 ( -5, -2) |
| [‡] This collapses MK-0249 doses of 10 and 12 mg. | |

# Conclusions

- Biased estimates due to
  - adaptation, bad doses biased down good doses bias up
  - truncated distribution used in NMAR and Mixture Missing Mechanism
- Inflated placebo estimates in 30% NMAR leads to huge loss in power
- Future work
  - pattern mixture model

# References

- Applied Longitudinal Analysis. Garrett M. Fitzmaurice , Nan M. Laird , and James H. Ware . Hoboken, NJ: Wiley, 2004.

- Anastasia Ivanova, Ken Liu, Ellen Snyder, Duane Snavely. " An Adaptive Design for Identifying the Dose with the Best Efficacy/Tolerability Profile with Application to a Crossover Dose-Finding Study." Statistics in Medicine, (in press 2009).

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