ANALITICAL AND INTERPRETATION ISSUES IN EVALUATING ANALGESIC TREATMENT OUTCOMES

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TRADITIONAL ANALYSIS

- The most common method used to analyze pain clinical trials is to summarize data by a change in mean values that are then compared between treatment groups (central tendency analysis, CTA).

- CTA remains the preferred method for drug development purpose.

STATISTICAL VS CLINICAL SIGNIFICANCE

- Statistical significance depends on: sample size, variability and magnitude of the treatment effect.
- Statistically significant improvements may reflect clinically meaningless benefits.
- Determination of statistical significance must be supplemented by descriptions of the magnitude of pain reduction.

(Dworkin et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations.J Pain. 2008)

RESPONSE ANALYSIS

One method is constituted by the so called “response analysis” (RA) which is based on the determination of the proportion of patients who reported a clinically important improvement in their pain condition.

Farrar JT. What is clinically meaningful? Outcome measures in pain clinical trials. Clin J Pain 2000

INDIVIDUAL RESPONDER OUTCOME MEASURES

Besides making results more easily understandable, the goal of responder approach is to be:

- clinically relevant;
- closely related to the response of the patient;
- responsive to change.

ANALGESIC DATA ANALYSIS

DESIGN ISSUES

- Patients population
- Outcome measure
- Measurement scale

ANALITICAL ISSUES

- Response definition
- Repeated measurement
- Missing data

Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. Pain 2005

HOW TO MEASURE IMPROVEMENT

- Absolute pain intensity (API)
  (post treatment evaluation)
- Row score change (RSC)
- Percentage score change (%SC)

EXAMPLES

- Example 1: pain intensity at T0=9
  pain intensity at T1=7
  API >=5
  RSC= 2
  %SC = 22%

- Example 2: pain intensity at T0=5
  pain intensity at T1=3
  API <5
  RSC= 2
  %SC = 40%

RESPONSE DEFINITION

Various studies conducted on patients with cronic pain, have compared the performance of various definition of response with respect to an external evaluation of treatment benefit.

RESPONSE DEFINITION for chronic pain evaluated through 0-10 NRS

Row score change	1	2	>4
Percentage score change	<20%	>30%	>50%
Improvement	poor	minimally important	substantial

(Dworkin et al. Interpreting the clinical importance of treatment outcomes in chronic painclinical trials: IMMPACT recommendations. J Pain. 2008)

CPRA GRAPHS

Cumulative proportion of responders analysis (CPRA) graphs permit to compare the proportion of responders of two or more treatments for each possible cut-off of the outcome choosen.

Farrar JT, Dworkin RH, Max MB. Use of the cumulative proportion of responders analysis graph to present paindata over a range of cut-off points: making clinical trial data more understandable. J Pain Symptom Manage. 2006

EXAMPLE

Data come from a double blind controlled clinical trial on the efficacy of gabapentin vs placebo in the treatment of neuropatic cancer pain.

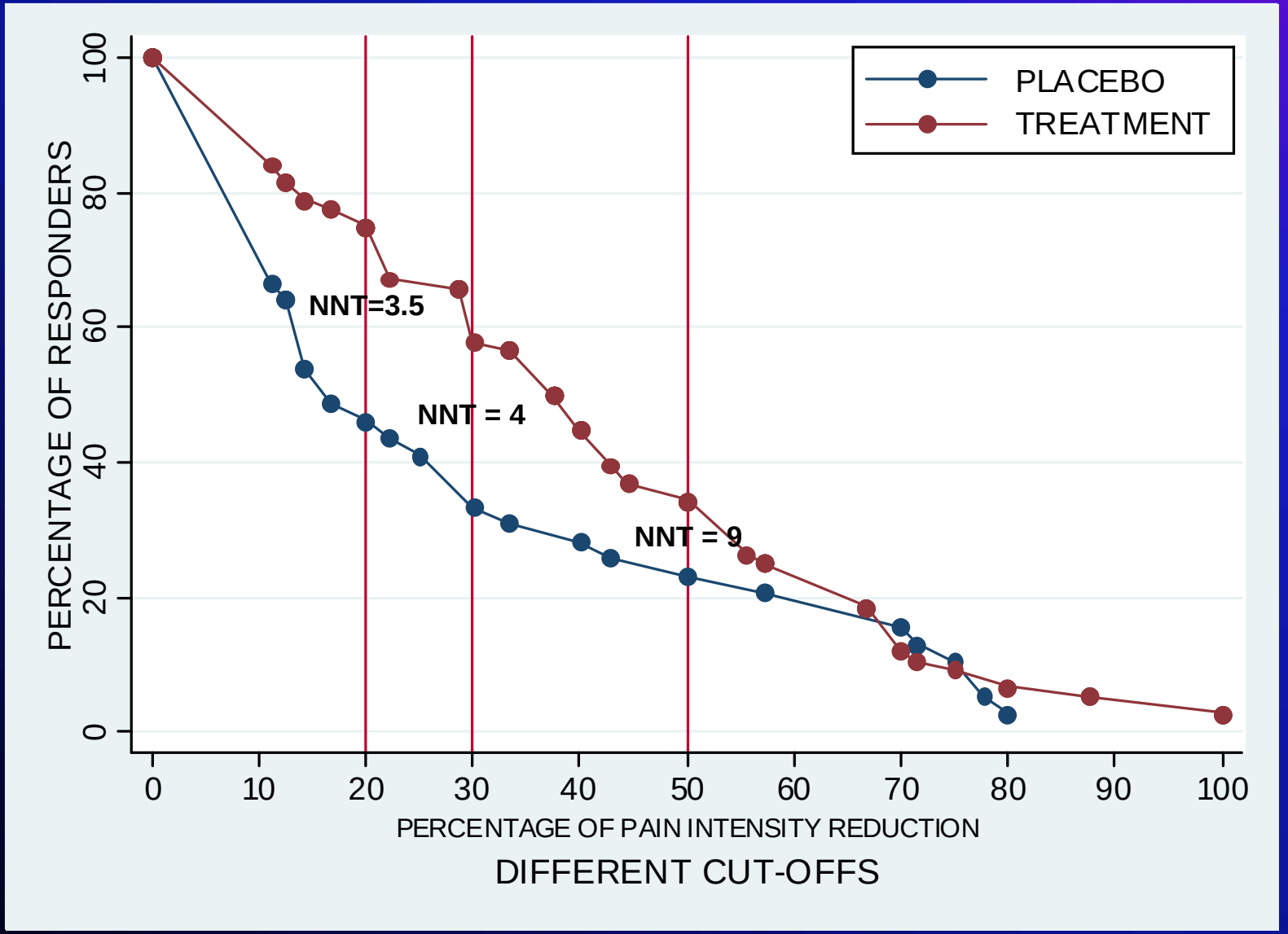
Pain intensity was evaluated on 121 patients through a 0-10 NRS at baseline and every day for the first 10 days of treatment.

Caraceni A, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the Gabapentin Cancer Pain Study Group. J Clin Oncol. 2004

CPR ANALYSIS OPERAZIONALIZATION AT DAY 3

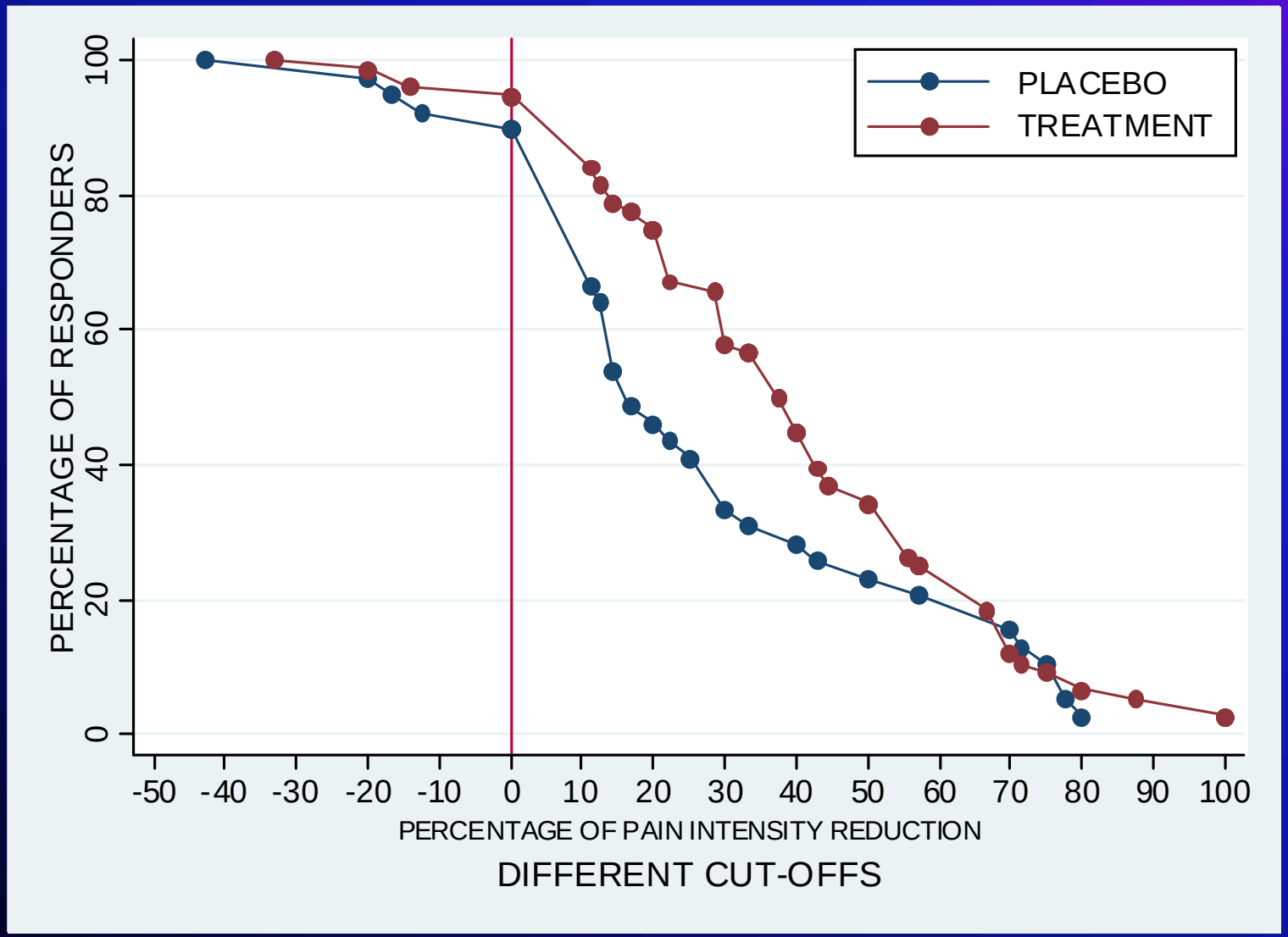
- For each patients the percentage of pain reduction from baseline and day 3 is calculated.
- For each level of response (0%-100%) the proportion of patients equaling or exceeding that level of response is calculated.
- Analysis is conducted separately for placebo and treatment groups.
- A two dimensional graph is created to display data

CPRA Graph at day 3



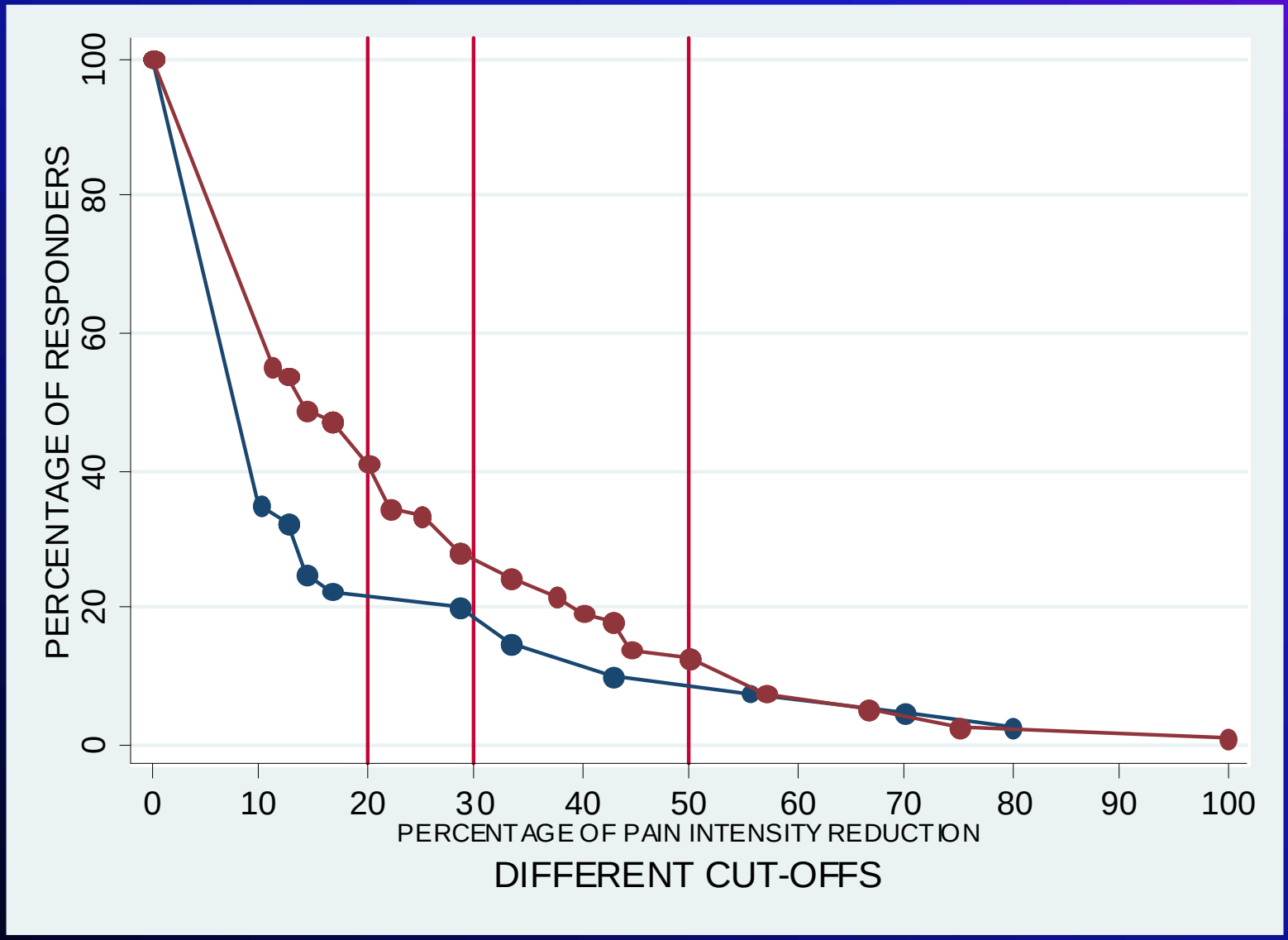
CPRA Graph at day 3

PATIENTS WORSENING

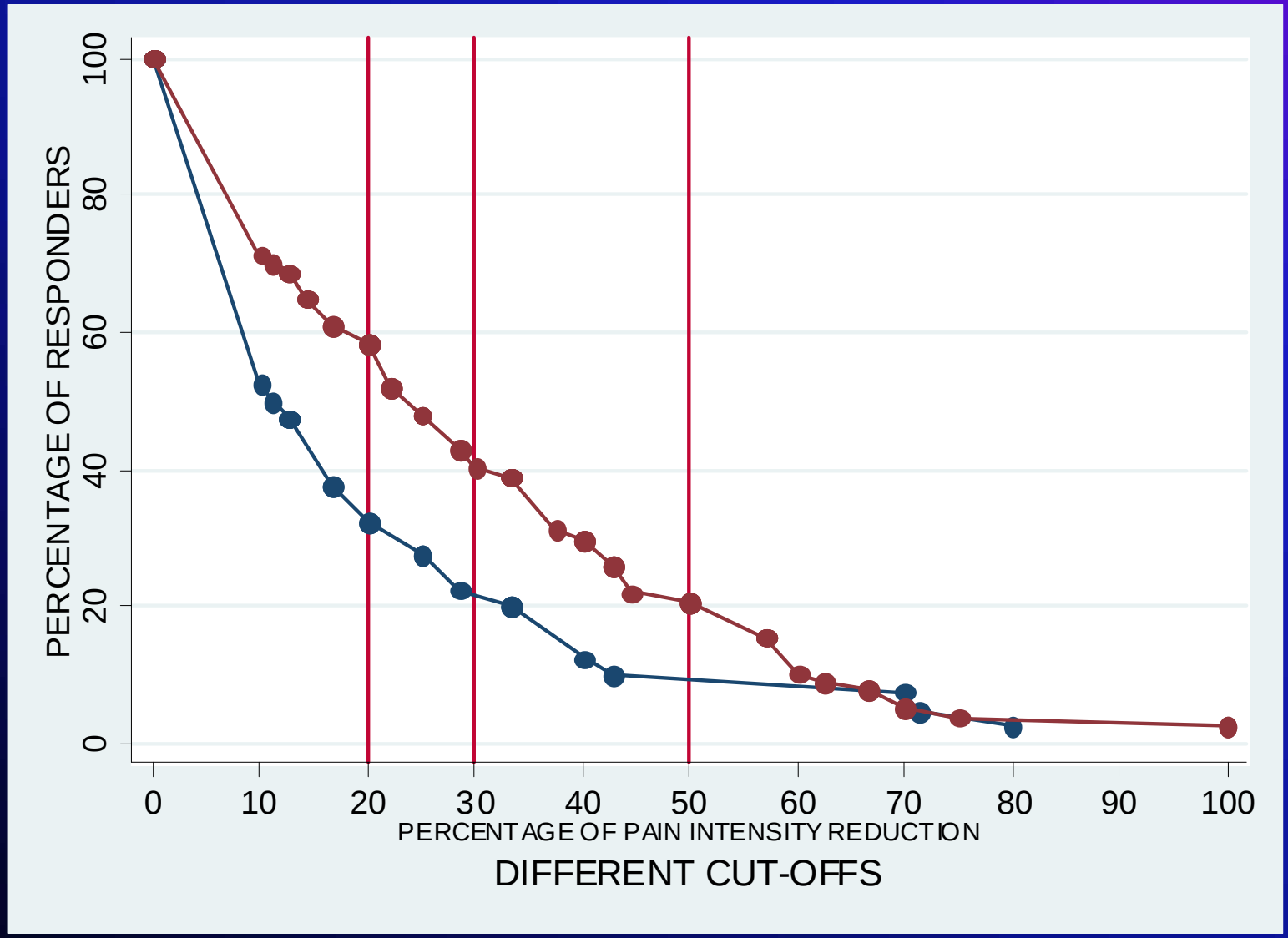


REPEATED MEASUREMENTS

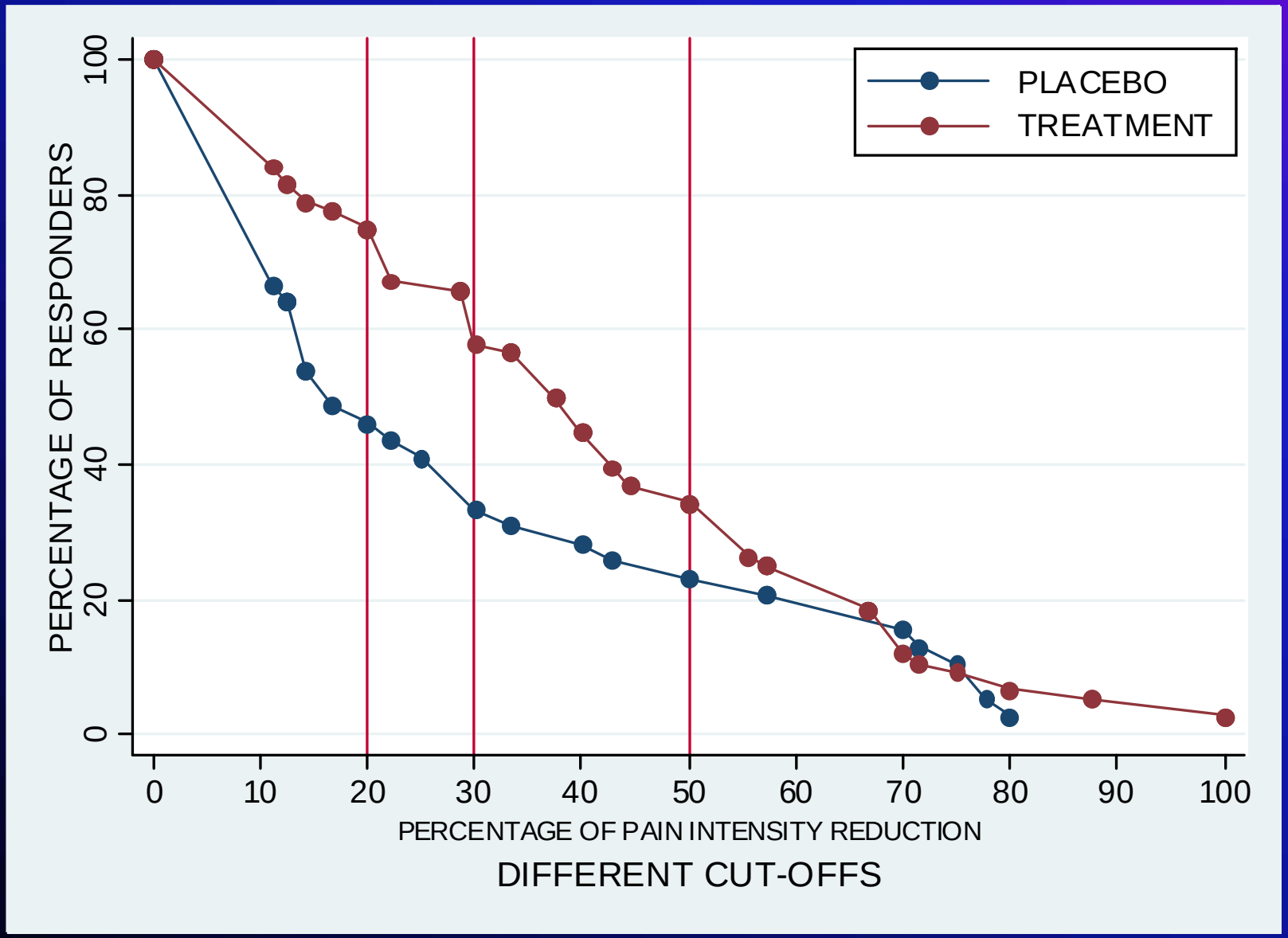
CPRA Graph at day1



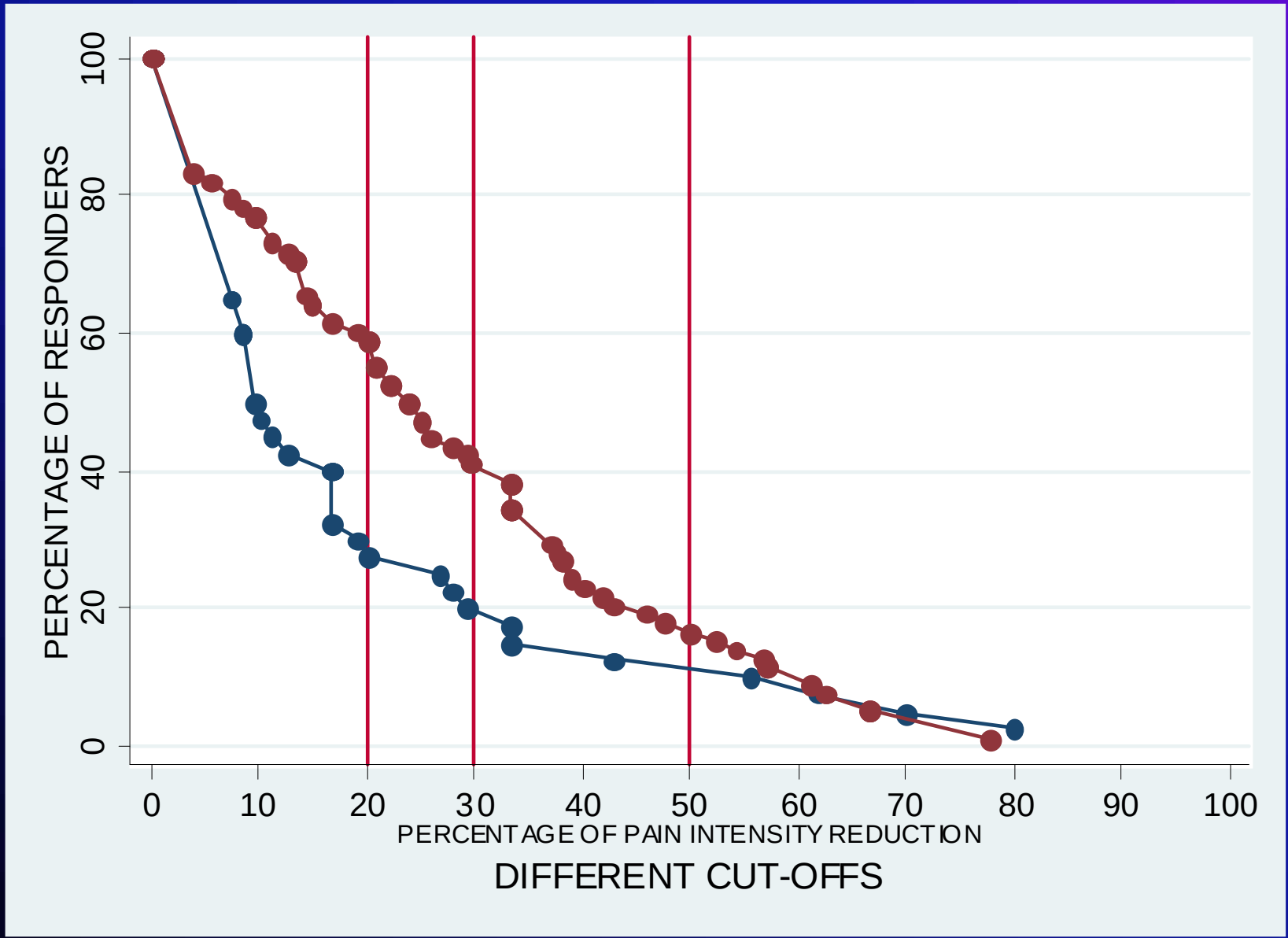
CPRA Graph at day2



CPRA Graph at day 3



CPRA Graph at days 1_2_3



CONCLUSIONS

Response analysis constitutes a simple, useful and effective method of data analysis but it requires that:

- the choice of the primary response definition is described a priori in the protocol analysis plan.
- sensitivity analysis (also possible through CPRA graphs) are conducted to support conclusions drawn from the primary analysis.

"... a difference is a difference only if it makes difference"

Durrel Huff, 1954

How to lie with statistics

New York, W W, Norton & Co 1954