

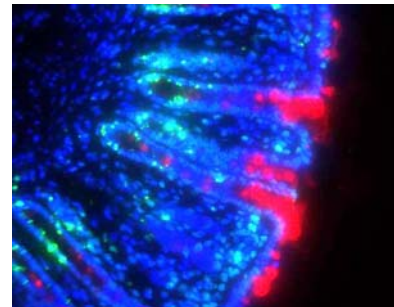
# LOCF and MMRM: Thoughts on Comparisons

**Raymond J. Carroll**

Texas A&M University

<http://stat.tamu.edu/~carroll>

[carroll@stat.tamu.edu](mailto:carroll@stat.tamu.edu)



# Outline

- Brief rehash of the talks comparing LOCF and mixed models
- Defense of LOCF as a **clinically relevant endpoint**
- Conclusions

## Bob O'Neill

- “In protocol planning, **assume** that monotonic missing data, if it occurs, is likely informative”, at least depending on treatment
  - At the very least, this means missing at random (MAR)
  - It makes no sense (to me!) to use as a primary analysis a method that is known to fail under the simplest MAR conditions.

## Bob O'Neill

- Problem: “how to specify in the protocol the primary strategy for dealing with missing data - if you presume that it will be informative - and you have not observed the data yet”
- “Decide what data will be collected that will allow for conditioning on factors that matter to address bias adjustments”
- **Message to me**: the more and better data that is gathered, the simpler the analysis that can be reasonably specified.

## Bob O'Neill

- “There is NO strategy which is adequate for all different combinations of dropout mechanisms, drop-out rates or less similar courses of disease and no adequate recommendations can be given”
- Amen!

## Bob O'Neill

- “Decide what data will be collected that will allow for conditioning on factors that matter to address bias adjustments”
- In addition, “If possible, collect data on all subjects until the trial is completed, even if withdrawn from trial”
- I’d say: try to collect data after dropout!
- The fact is that investigators can, with enough effort and expense, collect more data post dropout: a major point in what follows

# Geert Mohlenberghs and Craig Mallinckrodt: LOCF versus Mixed Models

- LOCF essentially never theoretically justified for endpoint and baseline comparisons, since as Bob O'Neill says, MAR or worse is the rule
  - Difficult to understand why it is used for this purpose
- Mixed Models are theoretically justified under readily explicated assumptions
  - Mixed model software makes it possible to write a priori defined protocols

# Review of LOCF versus Mixed Models

- Mixed models less sensitive to informative missingness (NMAR) than LOCF
- There is no single, nor can there ever be a single analysis for NMAR data (Bob O'Neill makes this point as well)
- Investigators should strive to collect data on dropouts, and follow them up.

# LOCF as a Clinically Relevant Endpoint

- One defense of LOCF is that it is **said to be** measuring a **clinically relevant endpoint**, albeit a different one from what MMRM is measuring
- We all know it is inappropriate for a endpoint/baseline comparison

# LOCF as a Clinically Relevant Endpoint

- One defense of LOCF is that it is **said to be** measuring a **clinically relevant endpoint**, albeit a different one from what MMRM is measuring
- That is, what is relevant is what **the physician sees** while the patient is in the study
- Thus, the argument goes, this is not a matter of statistics, it is a matter of medical science
- The argument sounds great, but is bogus

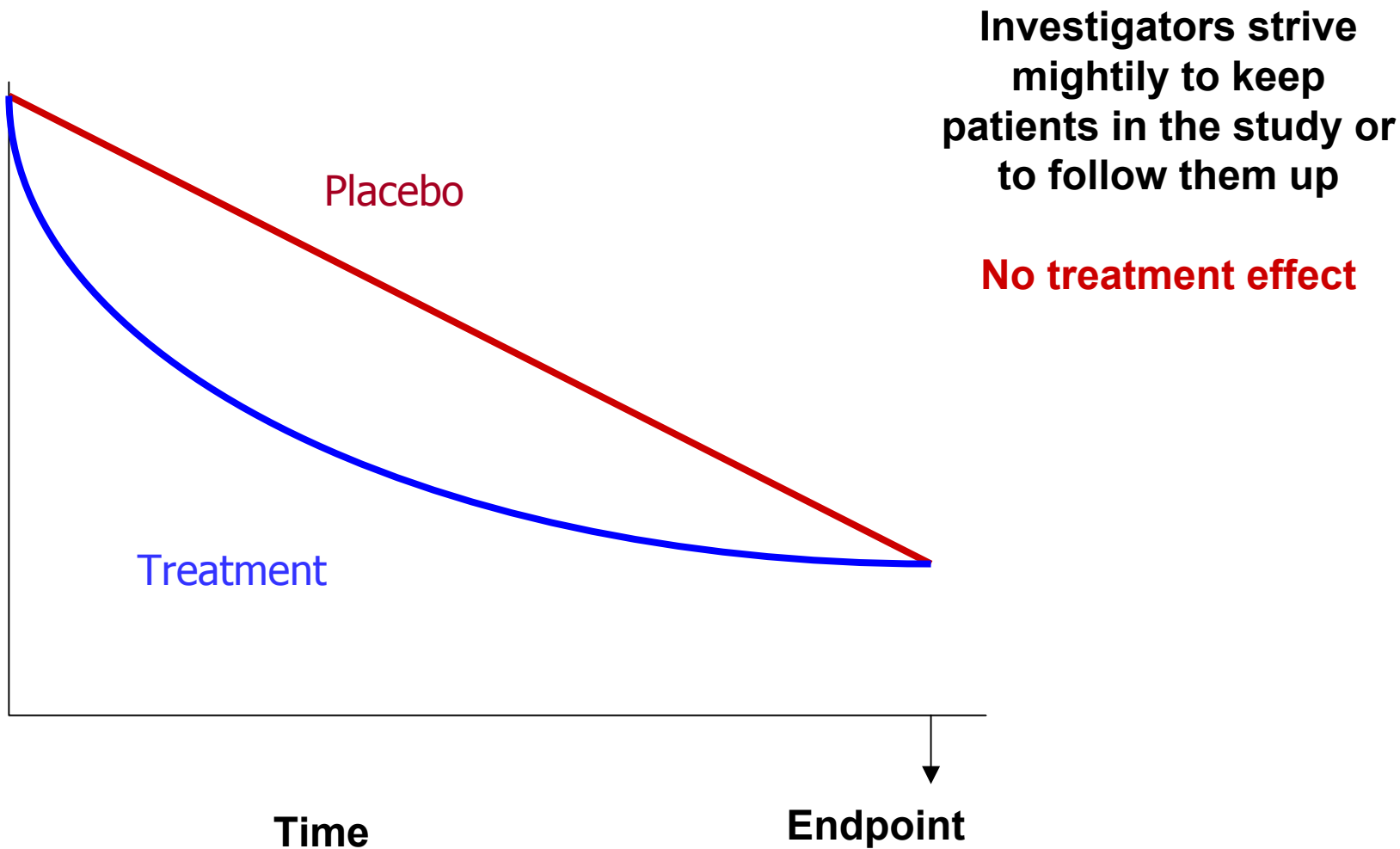
# LOCF as a Clinically Relevant Endpoint

- LOCF in this sense violates the fundamental basis of statistics
- When we compare populations, we compare them on the basis of a parameter
- LOCF has no physical parameter, because its result (mean change) is subject to investigator manipulation (More later)
- Thus, as a statistical method, LOCF makes no sense

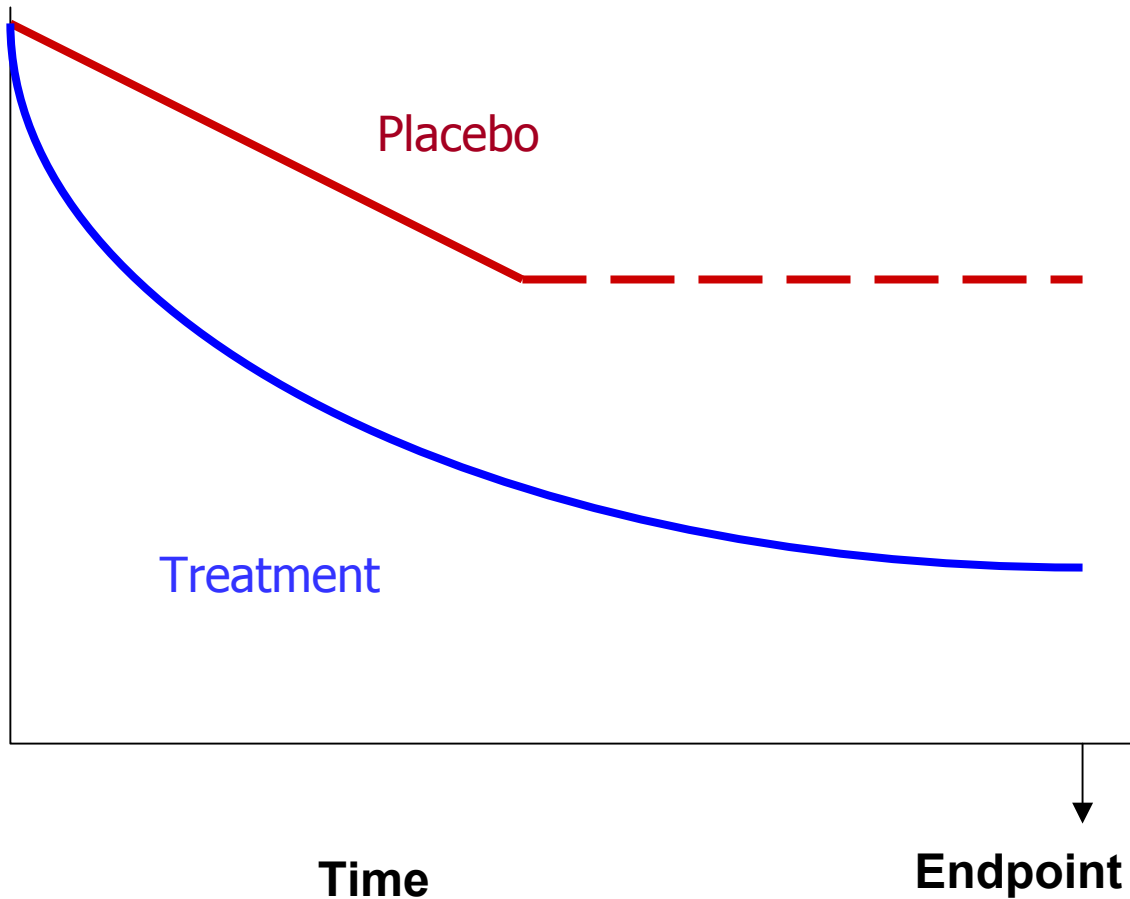
# LOCF as a Clinically Relevant Endpoint

- LOCF has no physical parameter, because its result (mean change) is subject to investigator manipulation
- Specifically, what LOCF measures differs depending on how much effort is spent in obtaining follow up data

# LOCF as a Clinically Relevant Endpoint



# LOCF as a Clinically Relevant Endpoint



Investigators skip follow up and lots of placebos drop out early (dashed line)

**Nice big treatment effect**

**What is LOCF making inference about? No one knows!**

# Conclusions

- Gather more data, either to make simpler analysis reasonable or to obviate need for NMAR analysis
  - Post dropout follow up?
- The “clinically relevant endpoint” argument for LOCF is all hat and no cattle
- No single NMAR analysis will ever exist