Exploratory Graphical Summaries of Longitudinal Concomitant Medication Data

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Today's Seminar

- Clinical trial overview
- Data collection for concomitant medications
- Present simplifying assumptions
- Define simple "Naïve" estimators
- Describe Mean Cumulative Function (M.C.F.)
- Present exploratory graphs a way to "look at" the con. Med. data
- Potential Uses

I. Concomitant Medications

- In a clinical trial, all medications other than study drug for the duration of patient participation in study.
- These may be prescriptions or patient self-reports
- Con. Med. Data may capture
  - Verbatim name and thesaurus “mapped” name
  - Start date/time or “continuing”
  - Stop date/time or “continuing”
  - Dose and route of administration
  - Reason: e.g. Administration due to an adverse event

II. Concomitant Medications

- Over a long time period, a single Con. Med. May be reported multiple times “recurrent”
- Computer processing to “link” records may be complicated, and in some situations manual review of each linked record may be required.
- In chronic or life threatening illnesses, con. Med. Data can be extensive and –messy-.
- Large amounts of data, difficult and expensive to ‘clean’

Standard Summaries of Con. Meds.

- Despite the longitudinal nature of con. Med. Data collection, the summaries are generally “incidence type”, or “ever never” received.
- Longitudinal information is ignored
- Sometimes “data listings” are provided to examine ‘longitudinal’ features
- No graphical method to “look” at the Longitudinal data

Randomized Clinical Trial

- A drug for a life-threatening condition
- Patients initially hospitalized and undergo surgery
- Patients either die, or are discharged from hospital
- Patients followed for 30 days or until death.

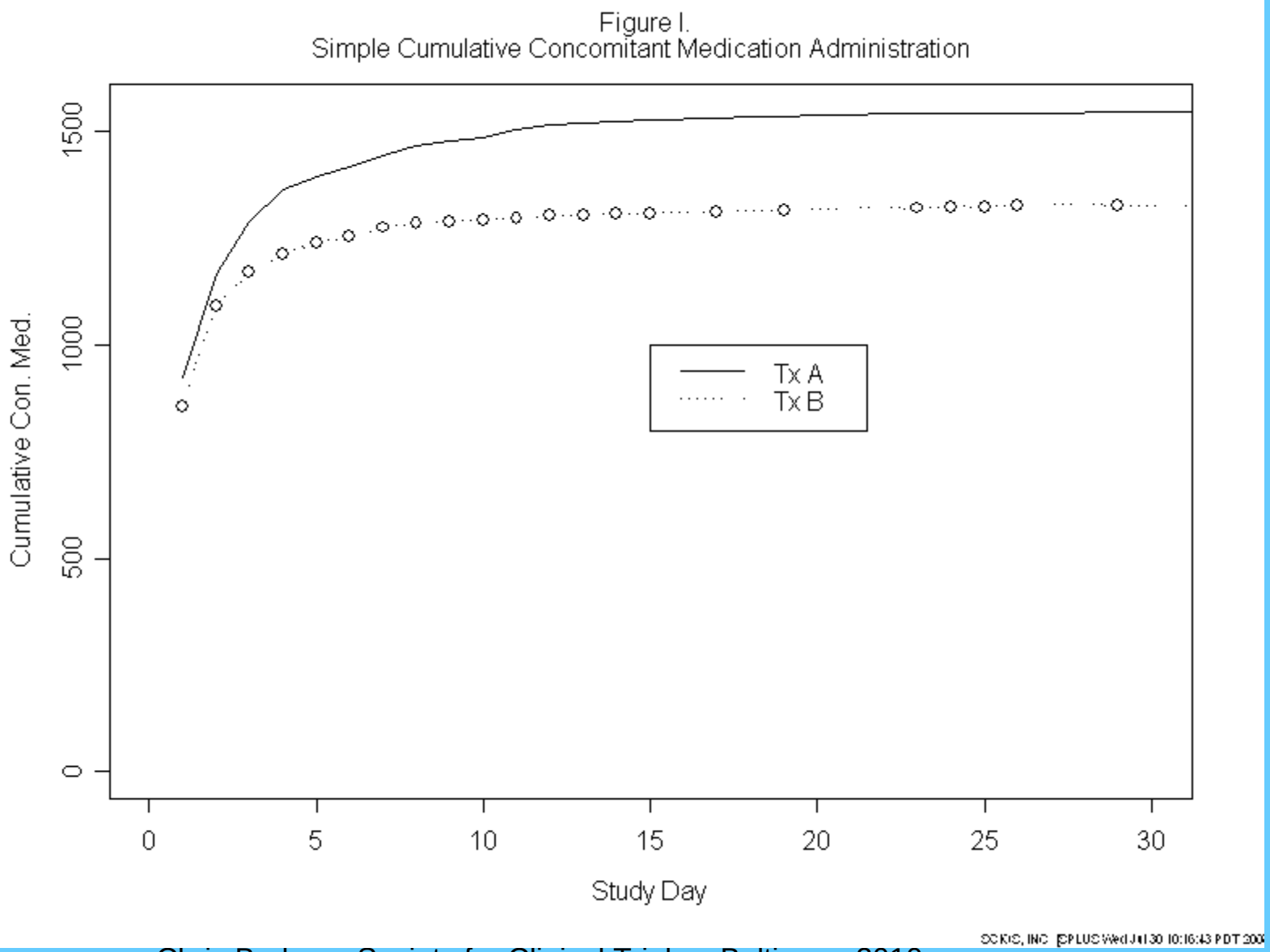
Simplifying Assumptions

- To demonstrate the estimators the following simplifying “non-statistical”assumptions were adopted
- There is one type of concomitant medication
- All reports with a “start date” are used, including reports of dose changes
- Data taken “as is” no additional consistency checking prepared.
- Only 30 days of observation available for each patient
- No “drop outs” and no “losses”
- “randomly break ties in date/time”

“Naive” or Simple Cumulative Summary

- Day 1 - Med 1
- Day 2 - Med 2
- Day 5 - Med 3
    - Cumulative
- Day 1: 1
- Day 2: 2
- Day 3: 2
- Day 4: 2
- Day 5: 3

Simple “Naïve” Cumulative Summary”



Mean Cumulative Function (M.C.F.)

- Provides a summary and graphical display of longitudinal Con. Med. Data
- Provides CI's and statistical tests of differences between treatment groups
- Accounts for Drop-outs, losses
- Estimated using "SPLIDA" (Splus for Life Data Analysis") (many functions in SAS-JMP, SAS reliability modules and "R" version "RSPLIDA").

M.C.F. Statistical Assumptions

- Accounts for drop outs and losses
- Estimator with CI
- Statistical treatment in Excel style in textbook by Nelson

$$\bar{Y} \pm K_C (s_t^2 / N)^{1/2} = M^*(t) \pm K_C \{v[M^*(t)]\}^{1/2}$$

M.C.F. Statistical Assumptions

- 1) the population model is a population of uncensored cumulative functions,
- 2) these functions extend to any time of interest,
- 3) the distribution of the cumulative is assumed to have a finite mean,
- 4) the Mc(t) is a continuous function, and
- 5) this function has a derivative m(t)=dM(t)/dt where m(t) is the population mean rate,
- 6) the sample trajectories are a simple random sample from some population,
- 7) the censoring ages are assumed to be given,
- 8) the trajectories are assumed to be independent of their censoring ages, and 9) the times of recurrences and ends of history are known exactly and are distinct points on a continuous time scale.

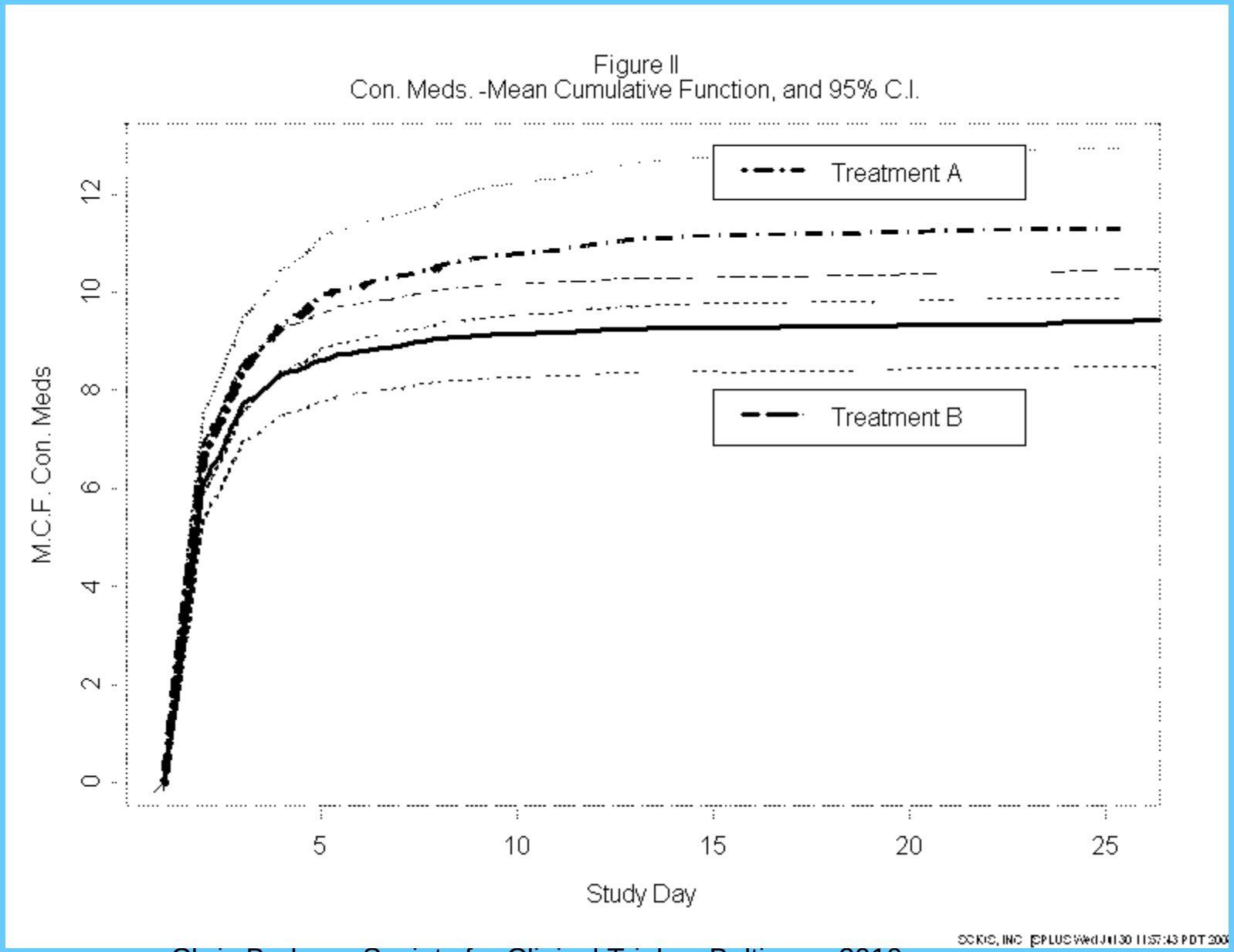
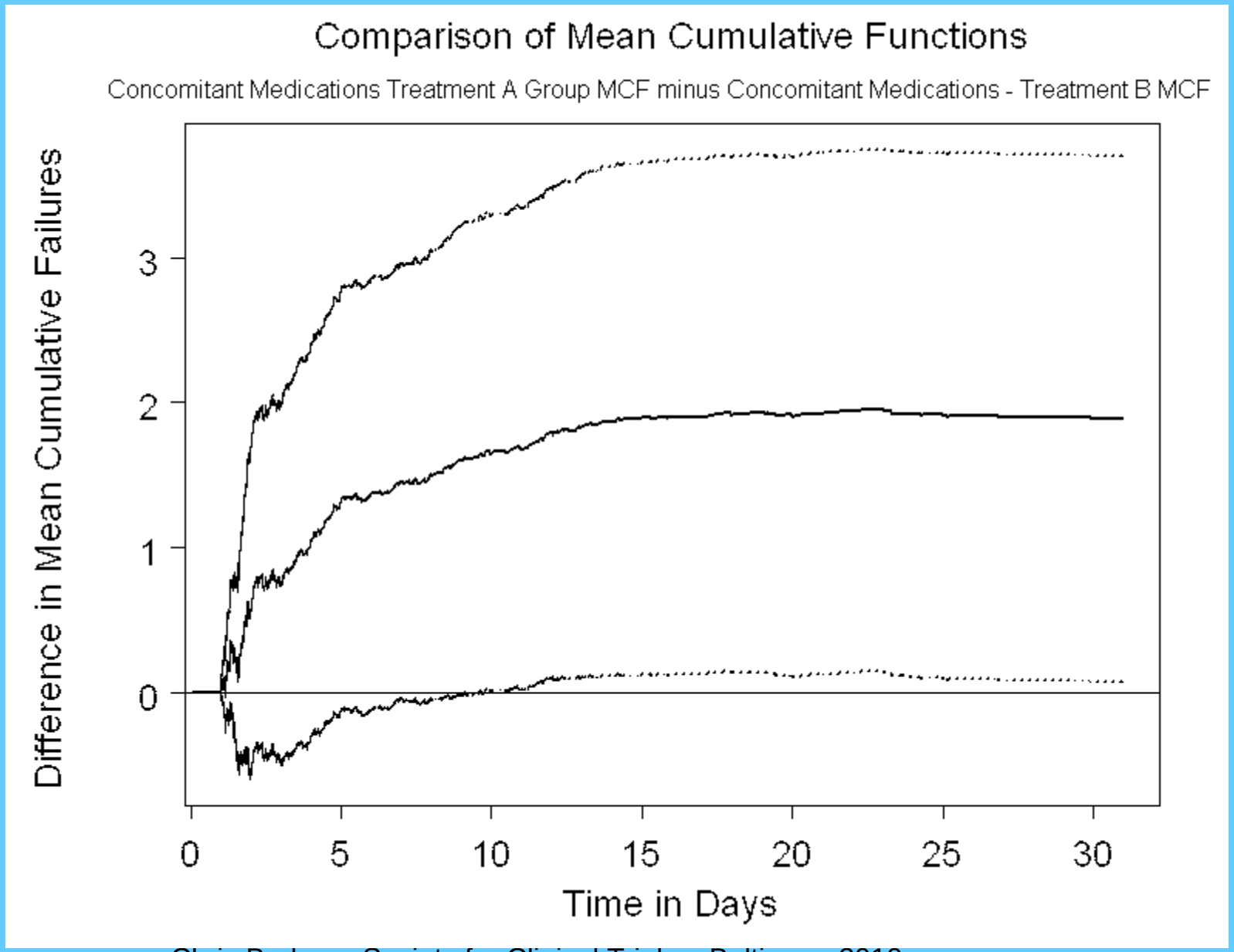


Figure II
Con. Meds. -Mean Cumulative Function, and 95% C.I.
Treatment A
Treatment B
M.C.F. Con. Meds
0
2
4
6
8
10
12
5
10
15
20
25
Study Day


Comparison of Mean Cumulative Functions
Concomitant Medications Treatment A Group MCF minus Concomitant Medications - Treatment B MCF
Difference in Mean Cumulative Failures
3
2
1
0
0
5
10
15
20
25
30
Time in Days

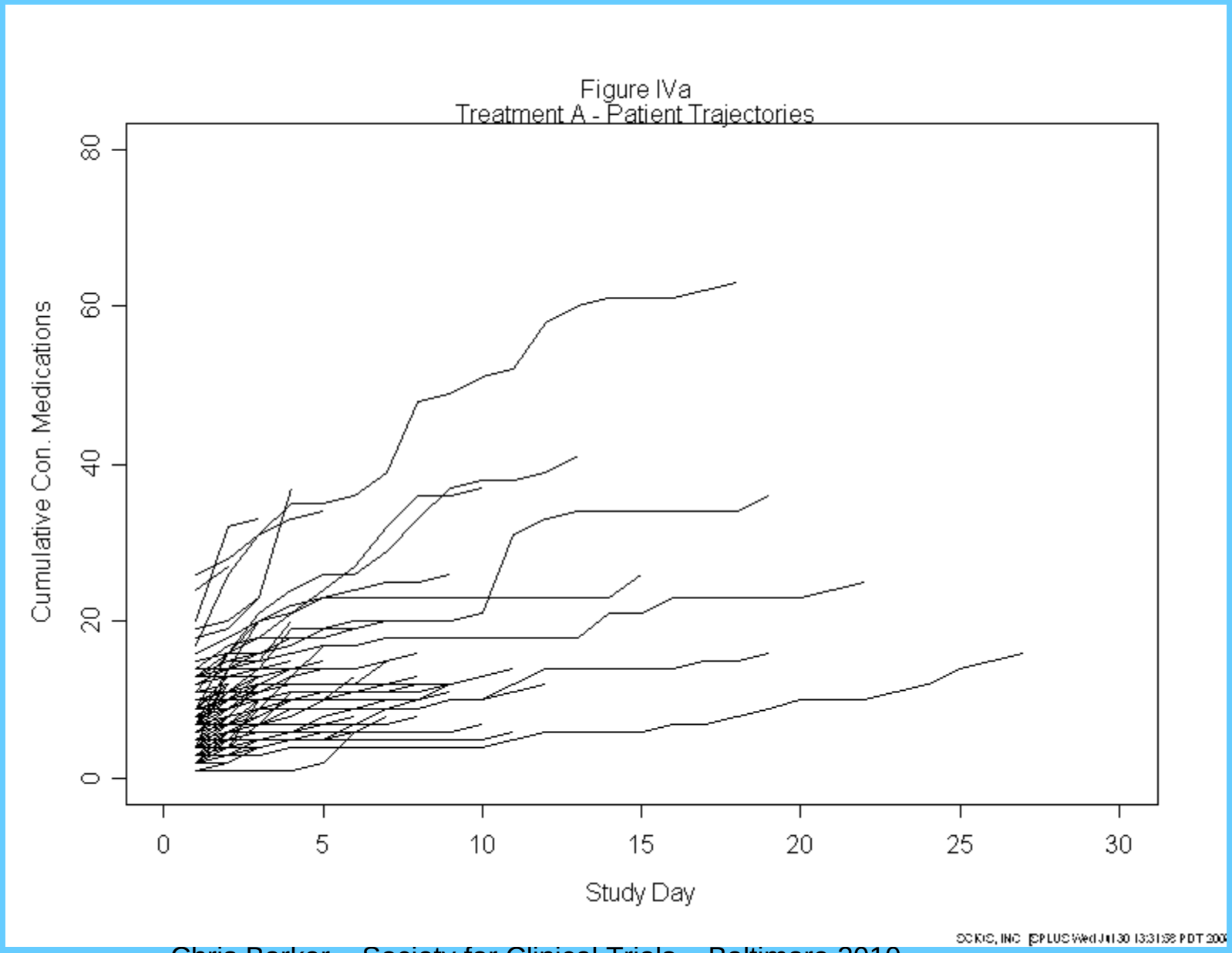


Figure IVa
Treatment A - Patient Trajectories
Cumulative Con. Medications
0
20
40
60
80
0
5
10
15
20
25
30
Study Day

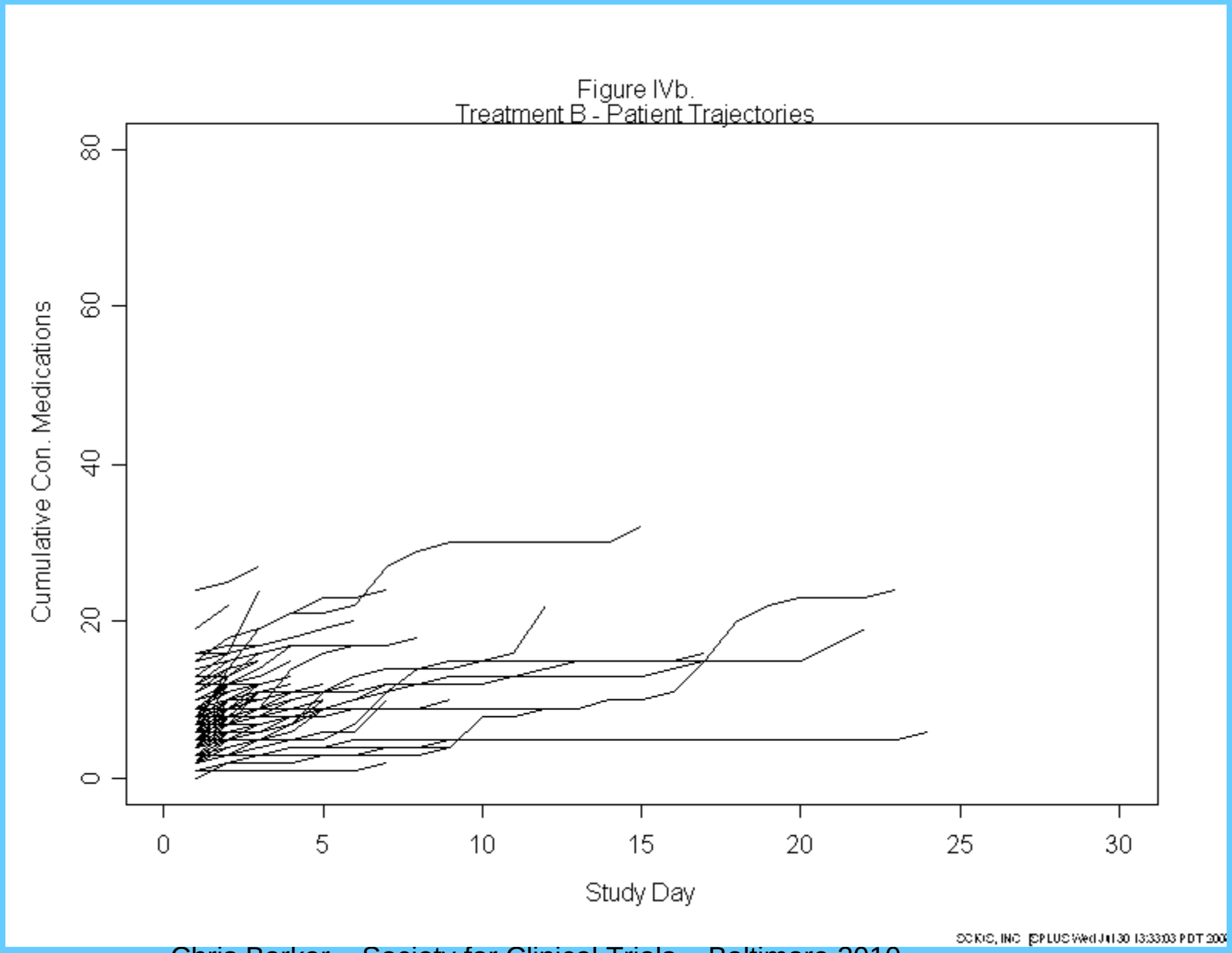
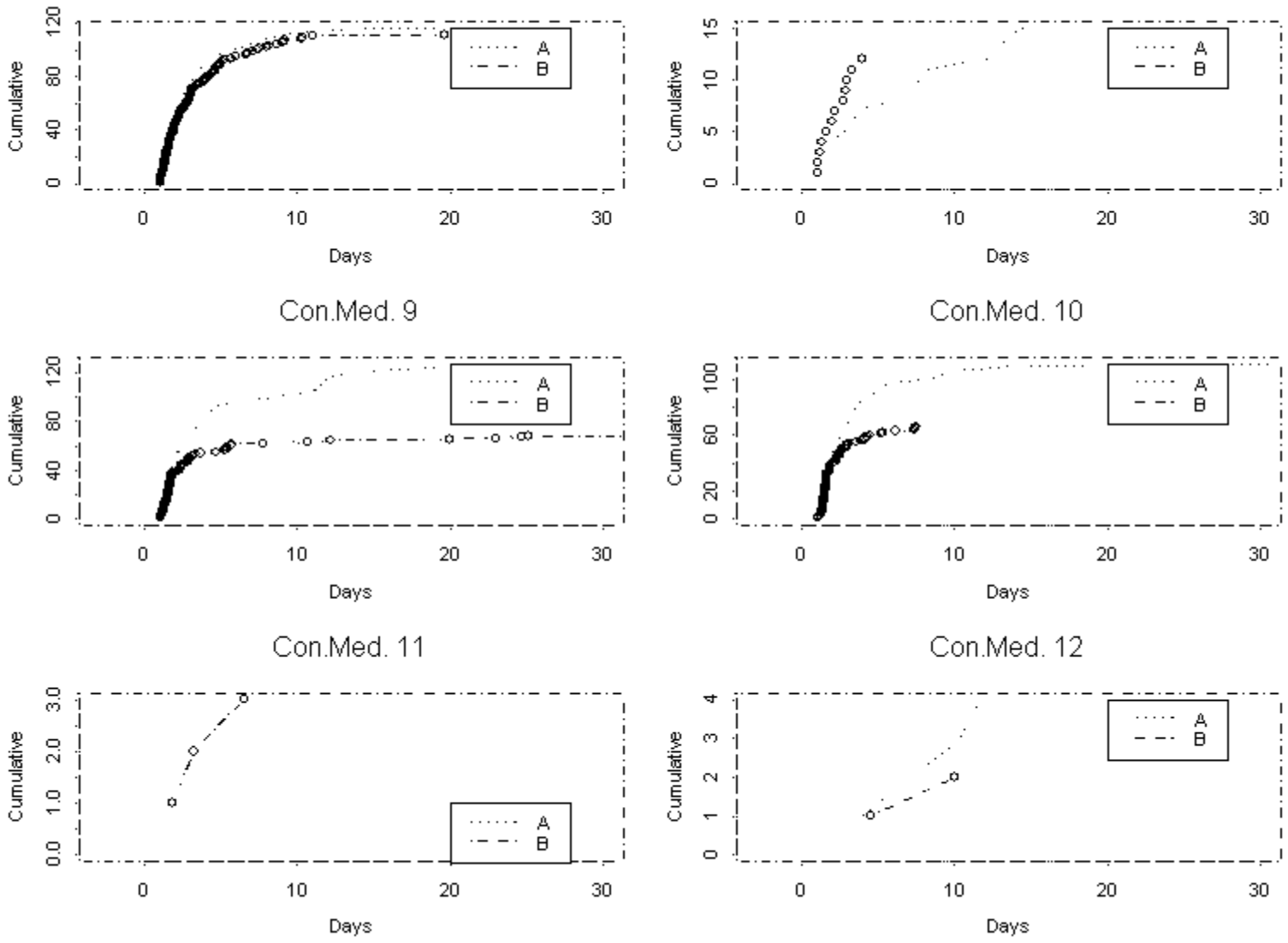


Figure IVb.
Treatment B - Patient Trajectories
Cumulative Con. Medications
0
20
40
60
80
0
5
10
15
20
25
30
Study Day

Figure


Con.Med. 7
Con.Med. 8
Con.Med. 9
Con.Med. 10
Con.Med. 11
Con.Med. 12
Cumulative
Days
A
B

The uses for summaries proposed here today

- Data monitoring and cleaning during an on-going trial
- Provide statistical tests of differences in longitudinal patterns of administration in a completed trial
- A graphical tool to “look” at the con. Med. Data

I. Conclusions

- Methods to Graphically Display Longitudinal Concomitant medication data
  - Naïve by treatment group
  - Patient Trajectories
  - Naïve by individual “preferred term” medication
  - M.C.F. By treatment group
  - Confidence intervals available to explore differences between M.C.F by groups
  - Difference estimator
  - Confidence intervals

II. Potential Uses & Next steps

- On-going review of accumulating data
- -data cleaning
- Test for differences between groups
- -remove simplifying assumptions
- Alternate analyses, e.g “mean cumulative dose” etc.
- Covariate adjustments

Bibliography

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- Doganaksoy, N. and Nelson, W. A method to compare two samples of recurrence data, Lifetime Data Analysis, 4, pp 5-63, 1998.