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

Figure I.
Simple Cumulative Concomitant Medication Administration

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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

\[
\bar{Y} \pm K_C (s_t^2 / N)^{1/2} = M^* (t) \pm K_C \{\sqrt{\hat{M}^* (t)}\}^{1/2}
\]
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.
Comparison of Mean Cumulative Functions

Concomitant Medications Treatment A Group MCF minus Concomitant Medications - Treatment B MCF

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Figure IVa
Treatment A - Patient Trajectories

Cumulative Con. Medications

Study Day

0 5 10 15 20 25 30

0 10 20 30 40 50 60 70 80

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Figure

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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 Concomitantly 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
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