PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. (2009)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/pst.395

Exploratory method for summarizing concomitant medication data – the mean cumulative function

CONSULTANTS' FORUM

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Concomitant Medications are medications used by patients in a clinical trial, other than the investigational drug. These data are routinely collected in clinical trials. The data are usually collected in a longitudinal manner, for the duration of patients' participation in the trial. The routine summaries of this data are incidence-type, describing whether or not a medication was ever administered during the study. The longitudinal aspect of the data is essentially ignored. The aim of this article is to suggest exploratory methods for graphically displaying the longitudinal features of the data using a well-established estimator called the 'mean cumulative function'. This estimator permits summary and a graphical display of the data, and preparation of some statistical tests to compare between groups. This estimator may also incorporate information on censoring of patient data. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: *mean cumulative function; SPLIDA; concomitant medications*

INTRODUCTION

This note presents a new application of an existing methodology for exploring and summarizing the longitudinal features of concomitant medication data collected in clinical trials. Two different longitudinal estimators with corresponding graphical displays are presented; the author recommends both. The first is a simple cumulative summary and the second is the Mean Cumulative Function (MCF). The MCF has multiple functions: (1) It estimates the cumulative number of administrations of concomitant medications; (2) It accounts for varying length of follow-up due to patient drop outs by censoring those data; (3) It allows computation of pointwise confidence bands; (4) It also allows the difference between treatment-specific MCF estimates in a randomized trial to be computed along with a confidence interval as a way to assess statistical significance of longitudinal changes.

The statistical tools and graphical display presented here are useful for the exploratory analysis of concomitant medication data in a

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clinical trial. Additional suggested uses may be for cleaning and monitoring the accumulating concomitant medication data during an on-going clinical trial.

Concomitant medication data are routinely collected in clinical trials. The collection of concomitant medication may occur throughout the time a patient participates in the clinical trial, and captures all medications used by the patient other than study drug. These medications may be self-reported by the patient, or recorded based on prescriptions from the study investigator. In addition to recording the verbatim name of the medication, the date, and possibly time the medication was started, and/or stopped, the dose, dose regimen, or changes in dose or regimen, possibly whether the medication was used to treat an adverse event may also be captured. In clinical trials of serious chronic illnesses, large amounts of concomitant medication data may be collected. This creates challenges to evaluating the role of concomitant medications on patient outcomes as well as issues of identifying and correcting discrepancies in concomitant medication data.

A common method of summarizing concomitant medication data is mapping the verbatim terms using a thesaurus such as WhoDrug. A common tabular summary of the data presents the incidence, that is, whether or not the medication was ever used during a study, similar to the summary of the incidence of adverse events. The simple incidence summary style does not permit a data reviewer to observe longitudinal patterns over time in the concomitant medications. A summary of longitudinal patterns should also account for patient drop out due to censoring or death for clinical trials involving chronic or life-threatening diseases.

In a clinical trial with a short duration, in which all patients are followed for the same fixed period of time after randomization, concomitant medication data could be summarized using the cumulative number of administrations of the medication during the study. This could be plotted versus the day post-randomization, and by treatment arm. The cumulative number may also be divided by the number of patients enrolled, to produce an interpretable 'per patient' value for the number of concomitant medications. A bootstrap confidence interval could be prepared to provide a method for making comparisons between groups. This simple cumulative estimate, without the bootstrap, is easy to prepare because it does not require specialized statistical software.

METHODS

For this note, concomitant medication and follow-up data are obtained from a randomized double-blind clinical trial in a post-surgical hospital setting, and the treatments groups are labeled as 'A' and 'B'. Patients were randomized to one of the treatments and followed for 30 days or until death. Study day is computed as day since randomization. The MCF is calculated and associated graphs are prepared using the SPLUS V7 package 'SPLIDA' [1] (Splus for Life Data Analysis). The concomitant medication data are combined with information on death or the end of the study and summarized using the MCF. An estimator of the difference between the MCF of the two treatment groups and graphical display are also presented.

Several important simplifications were made in this note for demonstrating this exploratory tool and these can be relaxed. The data in this example are from a completed clinical trial. The data are treated as if there were only a single type of concomitant medication and all medication reports are used in the exploratory analysis, including, for example, reports of dose changes. Each medication report is treated as a new administration. Ties in date–time of administration were broken by adding a value drawn from a uniform distribution and representing 1 min within a 24 h day. No attempt was made to re-evaluate the data for inconsistencies, for example, to determine whether the concomitant medication dosing information for a report (e.g. once, twice, or three times a day, etc.) is consistent with the number of records for that medication in the data set.

The reader is referred Nelson's book [2] for examples of the calculations for the statistics used

DOI: 10.1002/pst

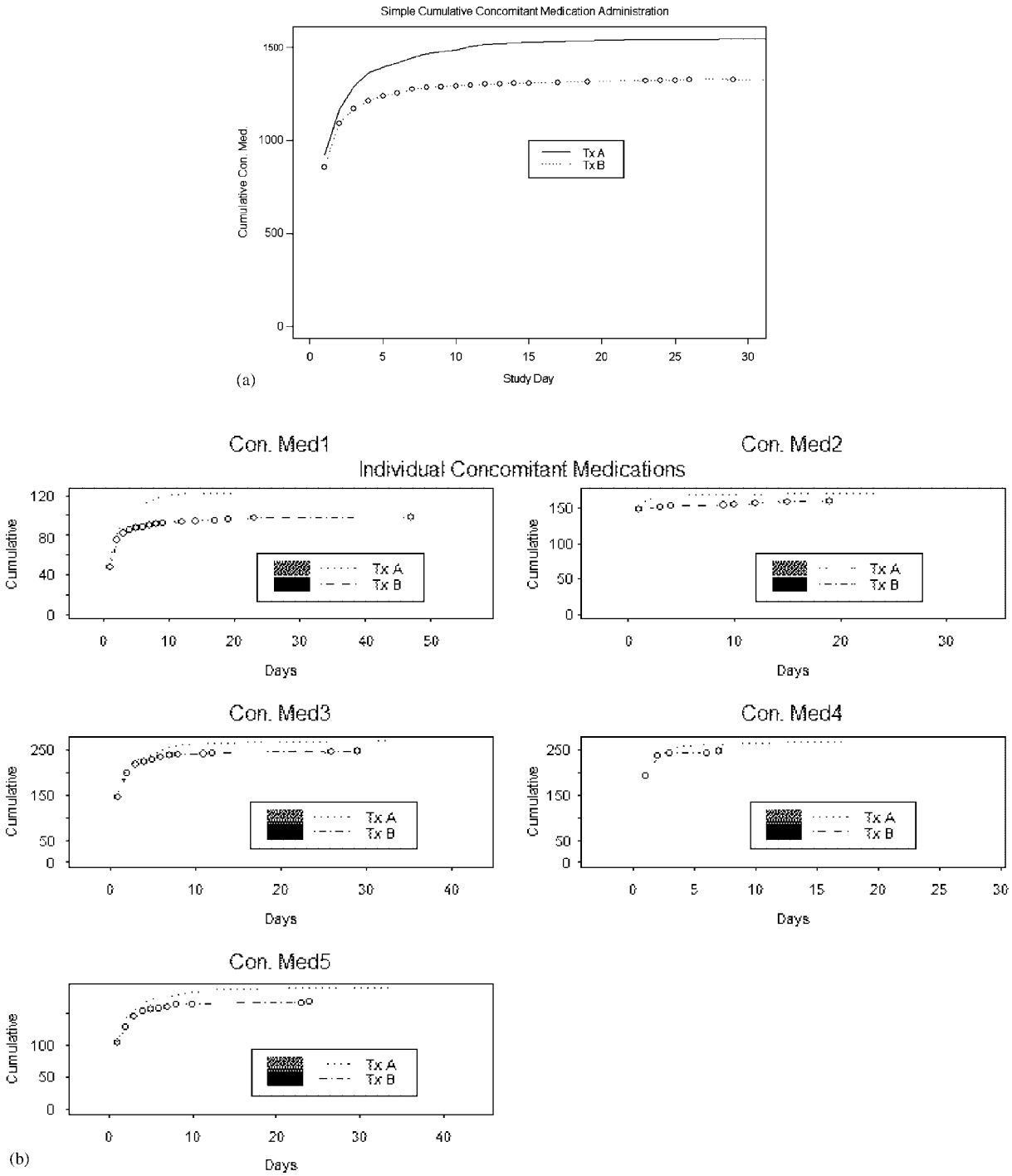

Figure 1. Simple summary. Simple cumulative summary by individual concomitant medications.

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in this note and presented in an elegant and simple Excel spreadsheet style; the use of formulae are limited. The estimator of the Mean Cumulative Function at time t is denoted as $M^*(t)$. The calculations for the MCF variance estimates and confidence intervals are computed using the methods described in Nelson [2] and are denoted as

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

where K_c is the $(100+C)/2$ standard normal percentile. An expression for the variance estimate of $M^*(t)$ is provided in the paper by Nelson [3]. This estimate is valid for uncensored observations. Nelson [3] derives the interval when the data include censored observations, using the following 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 $M_c(t)$ is a continuous function, and (5) this function has a derivative $m(t) = \mathrm{d}M(t)/\mathrm{d}t$ 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. The estimate of the difference between two MCF estimates and the confidence interval uses the methodology of Doganaksoy and Nelson [4].

The formula for the pointwise confidence limits for the difference are denoted

$$[M_1^*(t) - M_2^*(t)] \pm Z_c\{V[M_1^*(t)] + V[M_2^*(t)]\}^{1/2}$$

RESULTS

The data are 1330 concomitant medication reports from 141 patients receiving Treatment A and 1548 concomitant medication reports for 138 patients receiving Treatment B. The patients are initially in the hospital; follow-up continues after discharge. All concomitant medication data reported after randomization are used for these exploratory analyses.

The following sequence of steps are recommended by the author. Figure 1(a) is a simple cumulative summary by treatment group, counting every report of medication administration. It is easily prepared and may be a useful first step in an exploratory analysis because it does not require special statistical software. It may also be useful in the data cleaning and data monitoring stage of a clinical trial. A useful, additional exploratory analysis described below involves 'patient trajectories' – here defined as the simple cumulative summary of concomitant medication administration for an individual patient. Despite the fact that this simple methodology does not account for patient drop out or censoring, it may provide insights into the data. The plot suggests that concomitant medication use was higher in Treatment A. Figure 1(b) is a simple cumulative summary by a subset of the individual medications, to explore if one or more medications may have been used more in Treatment A than in B. These plots suggest that Medication 1 may have a greater increase than other medications. The simple cumulative is not standardized in any way by the number of patients, and the cumulative number of medications administered may not be an easily understandable number. Also there

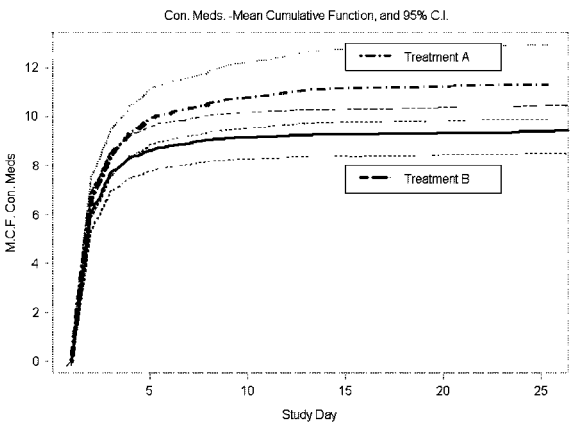

Figure 2. MCF estimates for concomitant medications treatment A and B and 95% confidence limits.

DOI: 10.1002/pst

are no statistical tests associated with this particular method of counting.

The next step is the estimation of the MCF that accounts for patient drop out and censoring. The MCF and the associated 95% confidence bands, estimated in SPLIDA, are graphically displayed for the two treatments in Figure 2, again, counting every report of administration of medication. The interpretation of Figure 2, for example at Day 20, suggests that the Treatment A patients had a mean cumulative administration of approximately 11 medications versus 9 in Treatment B.

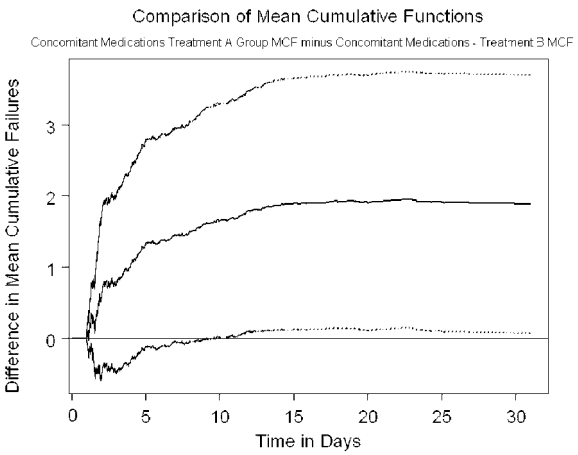

Figure 3. Difference of mean cumulative function and 95% confidence limits.

Figure 3 presents the summary of the difference between the two MCF functions with a 95% confidence interval. The cumulative number of concomitant medications is higher on Treatment A than Treatment B throughout the study period. For a period of time, beginning approximately on Day 11, the confidence interval excludes zero, which suggests a statistically significant increase for Treatment A. Statistical significance, in this exploratory analysis must be viewed with caution, particularly in light of the simplifying assumptions. Further analyses, for example, exploration of individual medications, may be appropriate to determine the reasons for the increase in Treatment A versus B.

Underlying the MCF are the individual patient cumulative summary, referred to as 'trajectories'. Figure 4(a, b) present a simple summary calculation within each treatment group, cumulate the medications for each patient, and displays the 'trajectory'. The trajectory plots for each patient may be difficult to distinguish in this mid-size clinical trial. A small section of the plot or a small number of patient's data could be displayed as 'exploded' in order to improve readability. In addition, the patient trajectory plot, possibly specialized to particular medications could be prepared during an ongoing trial and possibly used for data cleaning in addition to the simple cumulative summaries described above.

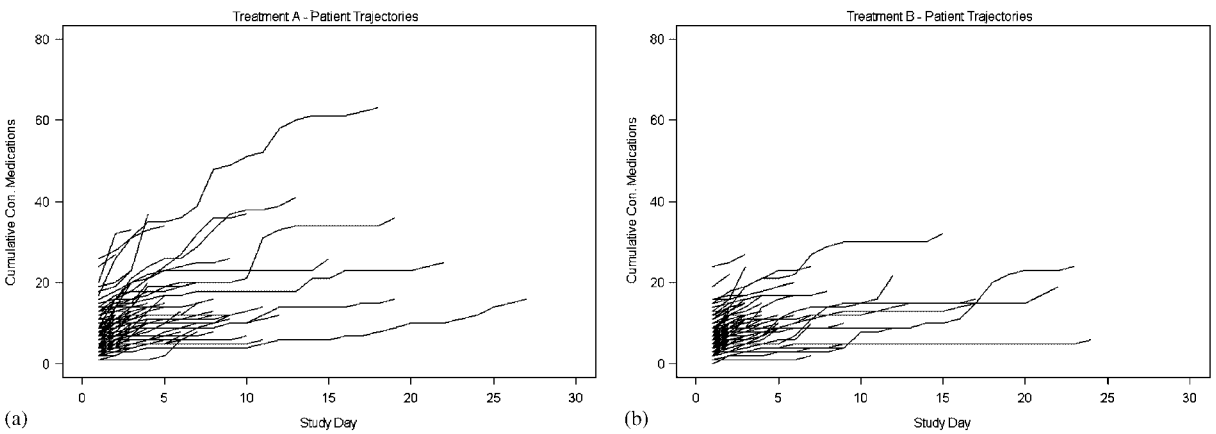

Figure 4. (a) Treatment A individual patient trajectories (b) Treatment B individual patient trajectories.

DOI: 10.1002/pst

A key observation of these patient level trajectory plots is that the patients vary in terms of the number of days they are administered medications, due in part to differences in follow-up.

DISCUSSION

The simple cumulative summary and some corresponding summaries at the patient level or at the medication preferred-term level may be useful for exploratory graphical analysis of concomitant medication data and for checking for unusual data during data cleaning of an on-going clinical trial. The simple summary does not require specialized statistical software. In a prospectively designed and randomized clinical trial, the MCF may be useful for extending the analyses of longitudinal concomitant medication data, for example by preparing statistical tests and unbiased estimates of differences between treatments in the cumulative administration of concomitant medications.

ACKNOWLEDGEMENTS

The author thanks the anonymous reviewers who provided very helpful suggestions. The author also thanks several colleagues for helpful discussions and comments during the preparation of this manuscript, in particular, Mei Cheng, Ann Olmsted, Robert Hoop and Whedy Wang.

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DOI: 10.1002/pst